A Study of the Fluorine Effect in C-H Borylation

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MSc Thesis

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2019

Abstract

Iridium-catalysed C-H borylation of fluoroarenes represents a very powerful method for the synthesis of fluorinated aryl boronic esters, which are a range of versatile synthetic building blocks. Following a brief review of the developments of Ir-catalysed C-H borylation reactions and synthesis of fluoroaromatics, this thesis describes the investigation of the influence of fluorine substituents on selectivity and effectiveness of iridium-catalysed C-H borylation of polyfluorinated arenes. As observed through the reactions of 1-fluoro-4-methylbenzene, 1-bromo-4-fluorobenzene, and other related substrates, simple fluoroarenes react considerably faster than their non-fluorinated counterparts. Polyfluoroarenes and fluorinated pyridines are even more reactive substrates. The fluorine atom is of low steric bulk and this coupled with a strong inductive electron-withdrawing effect leads to the activation of the C-H bonds *ortho* to a fluorine atom. However, with 1,3-difluoro-2-substituted arenes, as the electron-withdrawing nature of the 2-substituent increases there is a corresponding increase in the formation of the 1,3-difluoro-5-Bpin product. The parent arene, 1,3-difluorobenzene, shows variable selectivity depending on the nature of the boron source (B_2pin_2 and HBpin) and this observation challenges the accepted catalytic cycle for these reagents for which the key C-H activation step is supposed to be common. The resulting fluorinated aryl boronic esters can be used in the synthesis of fluorinated biaryls through Suzuki-Miyaura cross-coupling reactions using CsF as an anhydrous base to circumvent protodeboronation observed with more classical aqueous base conditions.

Contents

Abbreviations

aq.	aqueous
ASAP	atmospheric pressure solid analysis probe
Bn	benzyl
Boc	*tert*-butoxycarbonyl
B_2pin_2	bis(pinacolato)diboron
bpy	2,2'-bipyridine
ca.	*circa*
Cb	carbamate
cod	1,5-cyclooctadiene
coe	cyclooctene
conv.	conversion
COSY	correlation spectroscopy
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
dba	dibenzylideneacetone
DCM	dichloromethane
DMA	dimethylacetamide
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
dmpe	1,2-bis(dimethylphosphino)ethane

DMSO	dimethyl sulfoxide
D*o*M	directed *ortho* metalation
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenyl-phosphino)ferrocene
dr	diastereomeric ratio
dtbpy	4,4'-di-*tert*-butyl-2,2'-bipyridine
ee	enantiomeric excess
eq.	equivalents
ESI-MS	electrospray ionisation-mass spectrometry
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
GC-MS	gas chromatography-mass spectrometry
h	hour
HBpin	pinacolborane
HMBC	heteronuclear multiple bonds correlation
HSQC	heteronuclear single quantum coherence
Hz	Hertz
Ind	indenyl
*i*Pr	*iso*-propyl
IR	infrared radiation

LC-MS	liquid chromatography-mass spectrometry
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
min	minute
mL	milliliter
mmol	millimole
m.p.	melting point
MTBE	methyl *tert*-butyl ether
m/z	mass/charge ratio
NOESY	nuclear Overhauser effect spectroscopy
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
ref.	reference
r.t.	room temperature
Silica-SMAP	silica-supported silicon-constrained monodentate trialkylphosphine
TBAB	tetra-*n*-butylammonium bromide
*t*Bu	*tert*-butyl
temp.	temperature
THF	tetrahydrofuran

TLC	thin-layer chromatography
TMS	trimethylsilyl

Statement of copyright

Declaration

The work described in this thesis was carried out in the Department of Chemistry at Durham University between October 2017 and September 2018 under the supervision of Professor Patrick G. Steel. All the work is my own work, unless otherwise stated, and has not been submitted previously for a degree at this or any other university.

Mingyan Ding

December 2018

Acknowledgements

First and foremost, I would like to express my sincere gratitude to my supervisor Professor Patrick G. Steel for his guidance, encouragement and support in all the time of my MSc study.

I am grateful to all the members of CG1 for the fun we have had in the last year. Special mention goes to Jay for his assistance and advice in solving difficulties in my project, and to Courtney and Vanessa for proofreading sections.

My thanks and appreciations should go to the departmental service staff, especially Dr. Alan Kenwright for support in NMR analysis and Dr. Jackie A. Mosely for help with mass spectrometry.

I would also like to thank my parents who have provided me financial and emotional support throughout my life.

Last but by no means least, special thanks must go to my girlfriend Xirui, for all her love and support that helped me along the way.

1.0 Introduction

1.1 Introduction to this thesis

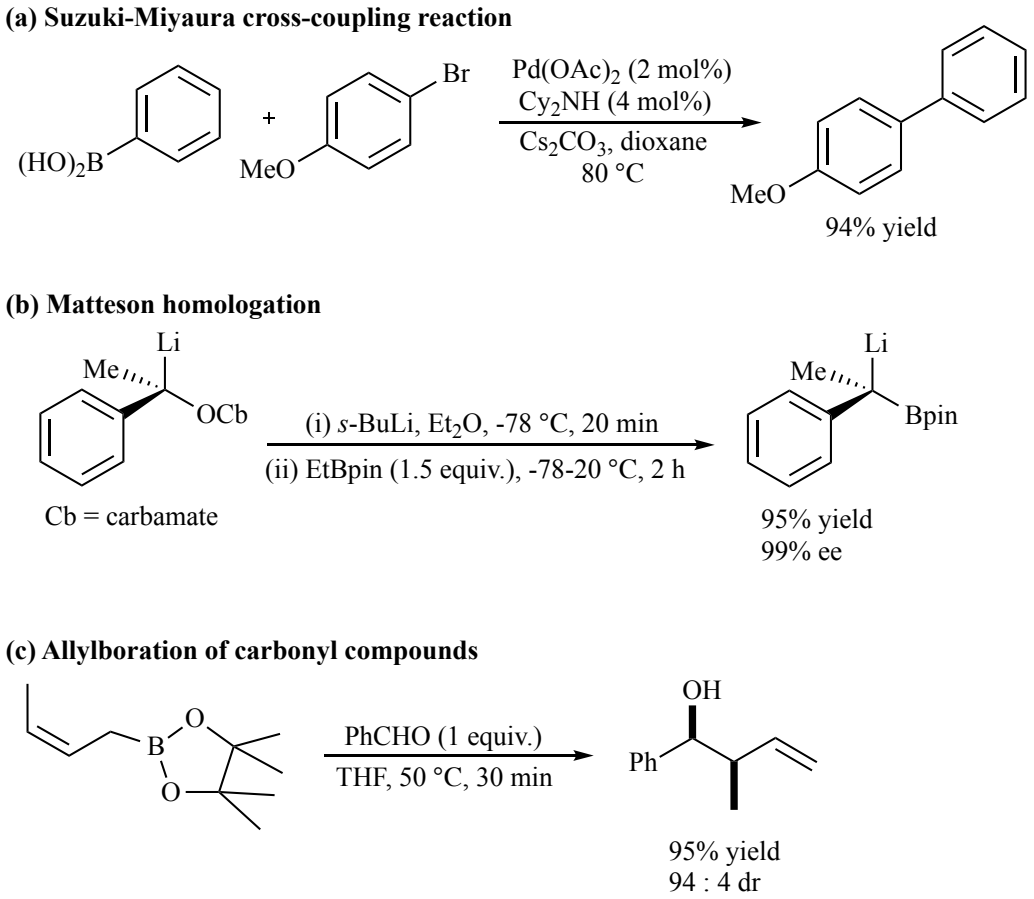
To date, aromatic organofluorine compounds have found diverse applications ranging from pharmaceuticals to agrochemicals due to their unique chemical, physical, or physiological properties afforded by fluorine substituents. For these molecules, cross-coupling reactions of suitable fluorinated aryl boronic precursors have been some of the most useful synthetic methods that can avoid the difficulties of late stage incorporation of fluorine atoms. Reflecting this, efficient methods for the synthesis of these fluorinated precursors would be valuable. In this thesis, the work directed towards this objective is described. This involves the preparation of fluorinated aryl boronic esters through Ir-catalysed C-H borylation of fluoroarenes, with the selectivity and effectiveness of this process being investigated. This thesis is divided into four main chapters. The remaining part of this chapter will provide a review focusing on areas most relevant to this project: C-H borylation and fluoroaromatics. Chapter 2 gives the results obtained in this study and the associated discussion and in the following two chapters, conclusions and future work, and detailed experimental procedures will be described respectively.

1.2 C-H borylation

1.2.1 Organoboron compounds

Organoboron compounds are a class of borane derivatives that contain a carbon-boron bond. Over the past half-century, organoboron reagents have been extensively studied

and applied in organic synthesis and catalysis because of their versatility and pivotal roles as synthons. The C-B bond can be easily converted to a C-C, C-N, C-O or C-X (X = Br, Cl) bond, as observed in numerous chemical transformations including the Suzuki-Miyaura cross-coupling reaction, Matteson homologation and allylboration of carbonyl compounds (Scheme 1).[1–3] Additionally, organoboron reagents have had an essential role in the pharmaceutical industry, as ^{10}B carriers for neutron capture therapy, in molecular imaging, and in material science and engineering.[4]



Scheme 1 Common reactions of organoboron compounds.[1–3]

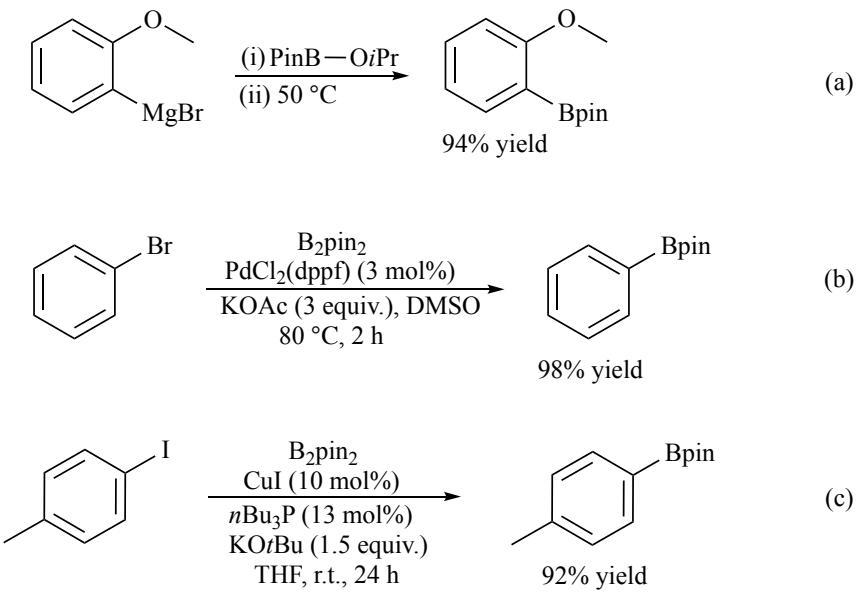
BR_3 boranes	BR_nH_{3-n} boron hydrides	$BR_2(OH)$ borinic acids	$BR(OH)_2$ boronic acids
$BR_2(OR)$ borinic esters	$BR(OR)_2$ boronic (boronate) esters	$RB(NR_2)_2$ boronamides	

Figure 1 Classification for organoboron compounds.

Classification for organoboron compounds in the reported literature varies greatly. However, they can be best categorised as boranes, boron hydrides, borinic and boronic acids, borinic and boronic esters, boronamides and other related compounds (Figure 1). Among these boron reagents, boronic (boronate) esters, which have fair stability to air, excellent functional-group tolerance, high compatibility with many reagents, and ease of purification and characterisation, are an extremely attractive class of chemical building block used in organic synthesis.[5] Moreover, due to their ultimate degradation into boric acid, boronic esters can be considered as environmentally friendly compounds of low toxicity.[5] Consequently, developing practical and efficient synthetic routes for boronic esters is of considerable current and future interest.

For the purpose of this thesis, only the synthesis of aryl boronic esters will be discussed. Traditionally, these compounds have been synthesised *via* the reaction of an organometallic species (Grignard or lithium reagent) with a borate ester (Scheme 2a).[6] Alternatively, routes containing palladium- or copper-catalysed borylation of aryl halides have been developed and widely employed (Scheme 2b and 2c).[7,8] These

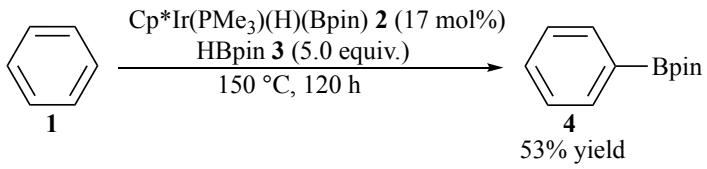
methods, however, have the drawbacks of limited functional group tolerance or the requirement of multistep synthesis. Recently, a direct iridium-catalysed C-H borylation strategy has emerged.[9–11] This provides access to aryl boronic esters under milder conditions in fewer steps and shows a high level of functional group tolerance. As such, this is the method of choice for the work described in this thesis. In this chapter, the developments of Ir-catalysed aromatic C-H borylation strategy will be described, along with the studies of mechanism and regioselectivity of these reactions.



Scheme 2 Traditional synthetic routes for aryl boronic esters.[6–8]

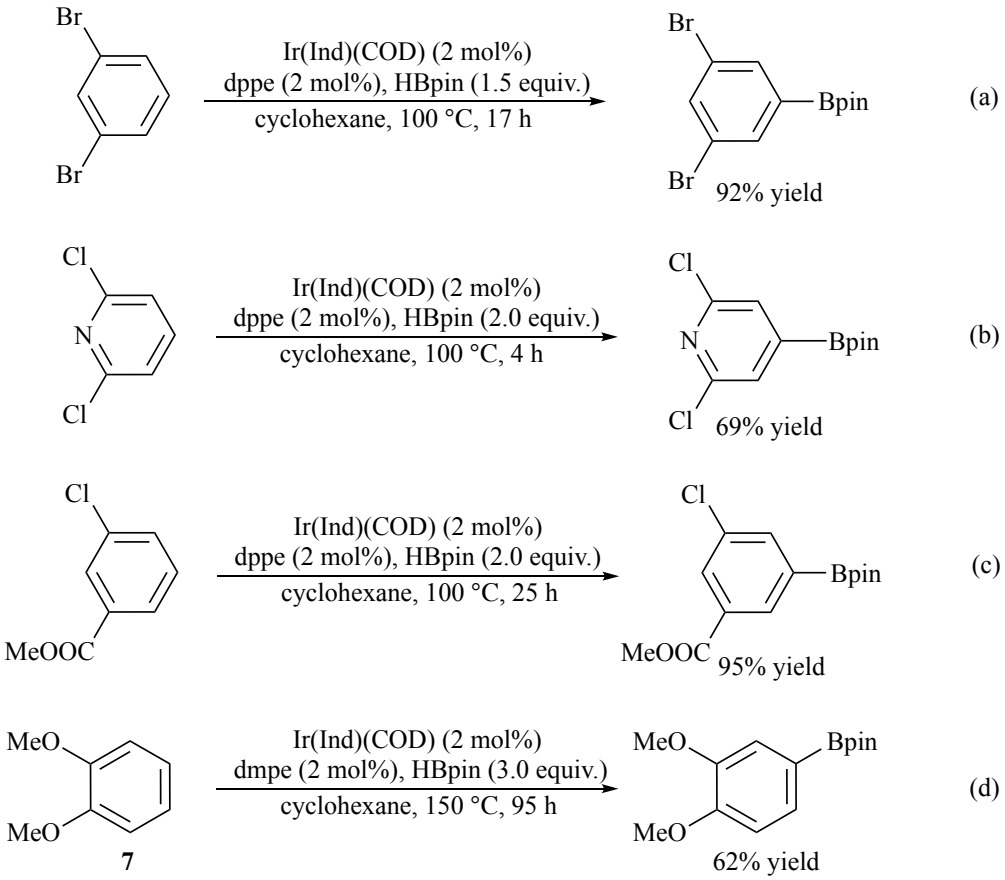
1.2.2 Discovery of iridium-catalysed C-H borylation

1.2.2.1 Early developments of iridium-catalysed C-H borylation



Scheme 3 First Ir-catalysed C-H borylation reaction for benzene.[12]

In 1999, Smith and Iverson reported the first catalytic C-H borylation reaction for benzene **1** using Cp*Ir(PMe_3)(H)(Bpin) **2** as catalyst and HBpin **3** (Bpin = pinacolborane) as boron source (Scheme 3).[12] After 120 hours at 150 °C, 3 catalytic turnovers were obtained affording C_6H_5Bpin **4** in 53% yield. Whilst the exact mechanism and intermediates are unknown, a comparative experiment of Cp*IrH_4 **5** and Cp*Ir(PMe_3)$(H)_2$ **6** suggested that the active catalyst contained a PMe_3 ligand.[9] The low turnover numbers afforded by Cp*Ir complex **2** limited the ability of this system and, to date, no reactions of arenes involving esters, amines, amides or of heteroarenes borylated with Cp*Ir(PMe_3)(H)(Bpin) **2** have been reported.



Scheme 4 Arene borylation catalysed by iridium-phosphine-systems.[9]

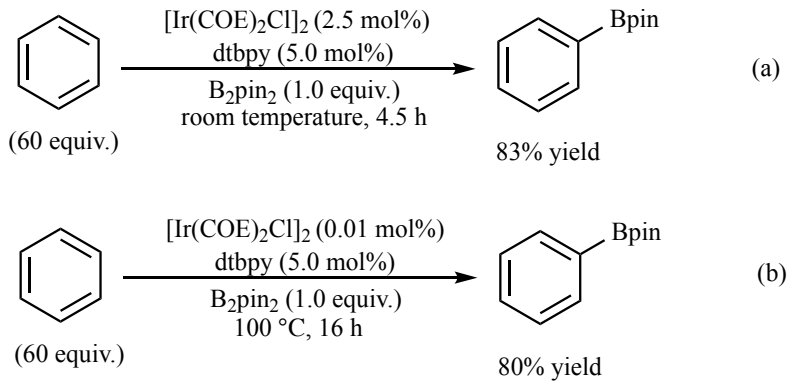
In 2002, a more efficient iridium-based catalytic system involving bisphosphine ligand was reported by Smith *et al.*[9] For example, whilst the borylation of benzene with HBpin at 150 °C using PMe_3 produced PhBpin in 88% yield after 18 hours, using systems with dmpe and dppe ligands produced 84% and 95% yields, respectively, after only 2 hours. Moreover, it proved possible to reduce the catalyst loading from 2 mol% to 0.02 mol% for the same substrate. This high efficiency of bidentate phosphine ligands was further demonstrated by reactions of a group of electron-deficient and electron-neutral arenes. Ester-, alkoxide- and halogen-substituted arenes and heteroaromatics were tolerated giving moderate to excellent yields (62% to 95%) (Scheme 4).[9]

These iridium-phosphine-catalysed borylation systems represented a significant step forward from the earlier works due to their faster reaction rates and reduced catalyst loadings. However, the temperatures required for these reactions remained high (100-150 °C) and short reaction times were not available for all arenes. For example, 95 hours were required to afford 62% borylated product from 1,2-dimethoxybenzene **7**, a more electron-rich substrate (Scheme 4d).

1.2.2.2 $[Ir(COD)X]_2$-bipyridines-catalysed borylation

Concurrently with the work on arene borylation catalysed by phosphine ligands-containing iridium complexes,[9] Ishiyama, Miyaura, Hartwig and colleagues[10] reported a catalyst system using iridium precursors and bipyridine ligands. These novel catalyst combinations were demonstrated to be more active than that with phosphine ligands,

not only lowering reaction temperatures to room temperature-80 ℃ (Scheme 5a), but also increasing turnover numbers to 500-1000 in many cases and even achieving 8000 in favourable cases (Scheme 5b).[10,13]



Scheme 5 (a) First catalytic C-H borylation at room temperature,[10] (b) Borylation with 8000 turnovers.[13]

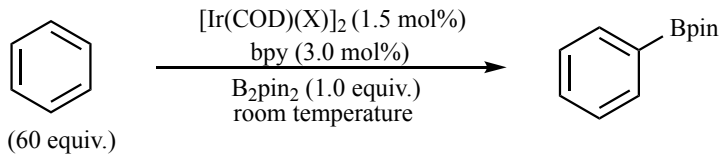
1 : 1 mixture of arenes	GLC yields ratio (%)
$PhCF_3$ **8** PhMe **9**	$PhCF_3$-Bpin **11** : PhMe-Bpin **12** = 90 : 10
$PhCF_3$ **8** PhOMe **10**	$PhCF_3$-Bpin **11** : PhOMe-Bpin **13** = 85 : 15
PhMe **9** PhOMe **10**	PhMe-Bpin **12** : PhOMe-Bpin **13** = 40 : 60

Table 1 Comparative studies for electron-poor and electron-rich arene substrates.[10]

In their initial work, a variance in the reactivity of electron-poor and electron-rich arenes given by this catalyst system was observed.[10] Electron-poor arene substrates were shown to have higher reactivity than the electron-rich ones in a series of

comparative experiments where $PhCF_3$ **8** and PhMe **9**, $PhCF_3$ **8** and PhOMe **10**, PhMe **9** and PhOMe **10** were mixed in an equimolar amount to yield the corresponding borylated products (Table 1).

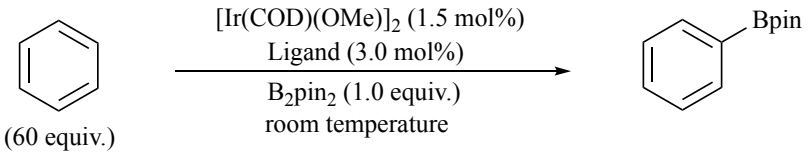
In order to optimize the iridium-bipyridine catalytic system, a systematic study of various anionic ligands (X) in the Ir(I)-COD precursor and bpy ligand was conducted in the presence of an excess amount of arene substrates by the same group.[11] Higher catalytic efficiencies were observed with more basic hydroxide- or alkoxide-containing iridium(I) complexes (**14c**, **14d**, and **14e**) (Table 2, entries 3-5) when compared to the corresponding halide **14a** (Table 2, entry 1), cationic **14b** (Table 2, entry 2) or acetate complexes **14f** (Table 2, entry 6). This was attributed to the easier formation of (boryl)iridium complexes, the key reactive intermediates in the catalytic process.



Entry	Ir(I)-COD precursor		Time/h	Conversion of B_2pin_2/%	GC yield/%
1	$[IrCl(COD)]_2$	**14a**	24	0	0
2	$[Ir(COD)_2]BF_4$	**14b**	24	3	0
3	$[Ir(OH)(COD)]_2$	**14c**	4	100	88
4	$[Ir(OPh)(COD)]_2$	**14d**	4	100	84
5	$[Ir(OMe)(COD)]_2$	**14e**	4	100	90
6	$[Ir(OAc)(COD)]_2$	**14f**	24	19	1

Table 2 $[Ir(COD)(X)]_2$ precursors with various anionic ligands.[11]

The influence of steric effects on the bpy ligand was probed through the introduction of methyl groups at various positions.[11] The lower activity of complexes containing 3,3'-dimethyl-2,2'-bipyridines **15c** (Table 3, entry 3) was proposed to result from increasing inhibition to the forming of a coplanar arrangement of the two pyridine rings. Moreover, the use of 6,6'-dimethyl-2,2'-bipyridine **15d** led to an inactive complex (Table 3, entry 4). This was attributed to the steric congestion around nitrogen atoms inhibiting coordination between ligands and iridium centres.



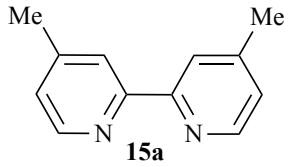
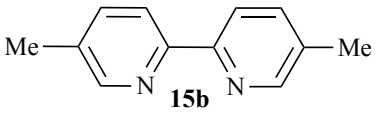
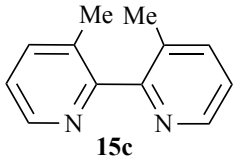
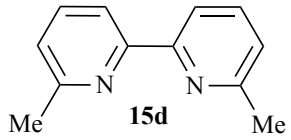
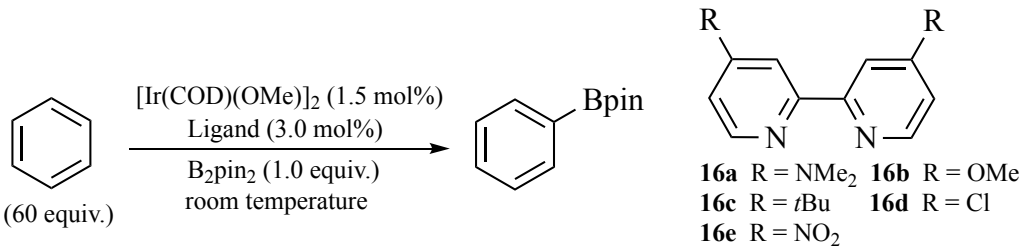
Entry	bpy ligand	Time/h	Conversion of B_2pin_2/%	GC yield/%
1	 **15a**	4	100	89
2	 **15b**	2	100	82
3	 **15c**	8	100	60
4	 **15d**	24	27	0

Table 3 Iridium catalytic systems containing dimethyl-2,2′-bipyridine ligands.[11]

Electronic influences on bpy ligands in arene borylation were also investigated by Ishiyama, Miyaura, Hartwig and co-workers, who disclosed that for arene borylation at room temperature, the reactivity with electron-donating functionalities (e.g. NMe_2, OMe and *t*Bu) (Table 4, entries 1-3) was superior to that when electron-withdrawing groups (e.g. Cl and NO_2) were present, which did not catalyse the reaction at all (Table 4, entries 4 and 5).[11]



Entry	Ligand	Time/h	Conversion of B_2pin_2/%	GC yield/%
1	**16a**	2	100	89
2	**16b**	4	100	90
3	**16c**	4	100	83
4	**16d**	24	16	0
5	**16e**	24	46	0

Table 4 Variation of 4,4'-disubstituted-2,2′-bipyridine ligand.[11]

Further advances in the utility of this protocol have included expanding the reaction scope from that conducted in neat arenes to ones that use more common organic solvents.[11] Experimental results showed that nonpolar solvents such as hexane conducted the reaction at a faster rate than more polar solvents such as DME and DMF. As the last part of this work, arenes with a variety of functionalities were tested and afforded moderate to high yields, indicating the versatility of this system.[11]

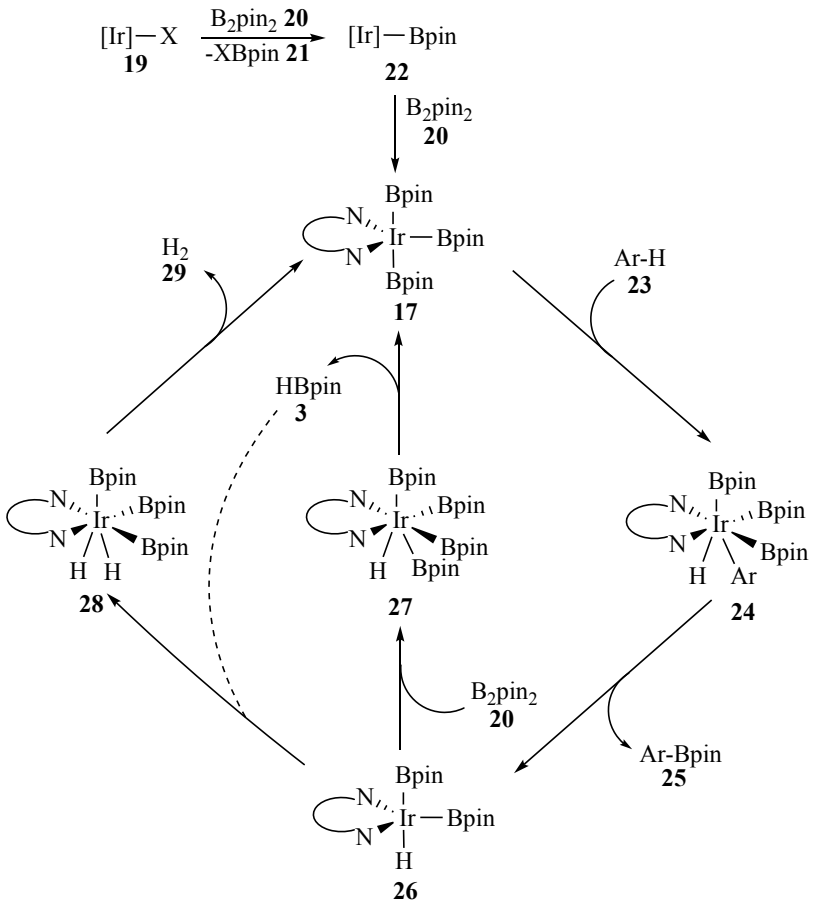
Since these papers, an iridium catalyst comprised of $[Ir(COD)(OMe)]_2$ **14e** and 4,4′-di-*tert*-butyl-2,2′-bipyridine **16c** has been widely applied in aromatic C-H borylation due to its high reactivity and compatibility at room temperature.

1.2.3 Mechanism of aromatic C-H borylation catalysed by Ir-dtbpy-system

The mechanistic pathway of arene borylation catalysed with iridium precursors and dtbpy ligand have now been extensively studied.[10,13–16] Key intermediates were initially speculated to be $[Ir(dtbpy)(Bpin)_3]$ **17** and its related Ir(III)-boryl complexes by Ishiyama, Miyaura and Hartwig *et al.*[10,13] In initial experiments, $[Ir(dtbpy)(COE)(Bpin)_3]$ **18** was successfully isolated, with its structure determined by X-ray diffraction.[10] The rapid formation of C_6D_5Bpin when **18** was dissolved in C_6D_6 suggested that this Ir(III)-boryl complex was competent to be a reactive intermediate in the catalytic system. Subsequently, more detailed studies showed that **18** gave similar yields and regioselectivities as $[Ir(COD)(OMe)]_2$ **14e** did in the borylation of arenes, indicating that iridium(III)-boryl complexes were the catalytically active species.[13]

Following this a general mechanism for arene borylation (Scheme 6) was proposed. The catalytic process starts after the reaction of Ir(I) complex [Ir(dtbpy)(X)] **19** and B_2pin_2 **20**, in which a trisboryl Ir(III) complex **17** is generated. The resulting trisboryl Ir(III) intermediate **17** then reacts with the arene **23** to afford the corresponding aryl boronic ester **25**. This latter process could occur either *via* an oxidative addition of **23** to yield an Ir(V) species **24** followed by reductive elimination of **25** to give rise to the

Ir(III)(Bpin)$_2$(H) complex **26**, or *via* a concerted σ-bond metathesis pathway which will afford the same functionalized product and Ir(III) hydride complex. The cycle is completed by the oxidative addition of **20** to afford [Ir(dtbpy)(H)(Bpin)$_4$] **27**, which later undergoes reductive elimination of HBpin **3** to regenerate the active trisboryl Ir(III) species **17**. Alternatively, another pathway from **26** to **17** involves the oxidative addition of **3** and H_2 **29** reductive elimination from an 18-electron Ir(V) species **28**. In this two-cycle model, fast consumption of B_2pin_2 occurs first followed by the slower borylation with HBpin.



Scheme 6 Proposed general mechanism for Ir-catalysed aromatic C-H borylation.[10,13,14]

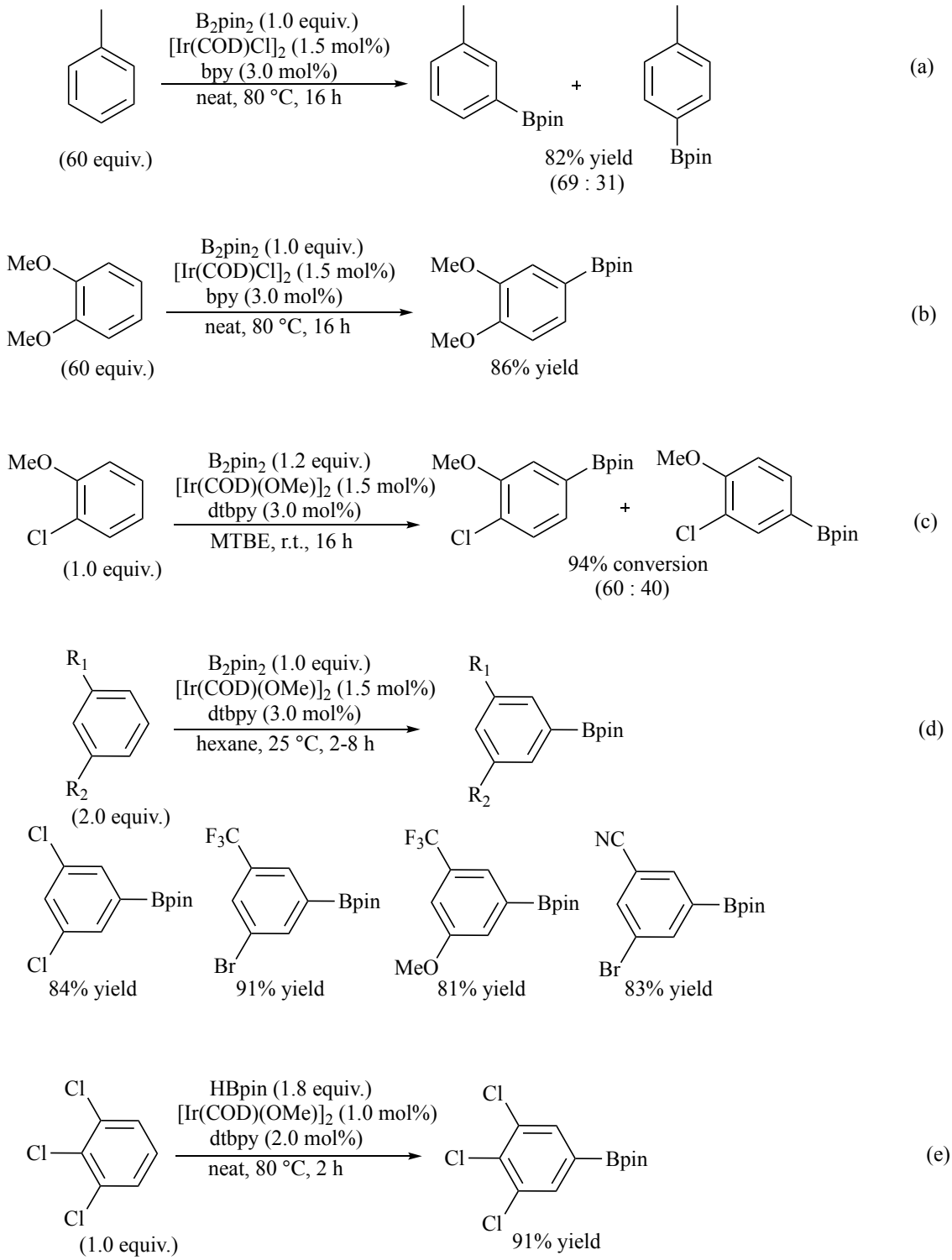
Sakaki and collaborators[14] then published further theoretical elucidation of this catalytic cycle, which was consistent with the results of experimental investigations.[13,15,16] In Sakaki's studies, the electron-donating effect to the metal centre from dtbpy ligand and diboron reagent as well as the small steric hindrance in the planar structures of dtbpy and B_2pin_2 facilitates the oxidative addition process and stabilizes the Ir(V) complex **24**. Besides, less bulky arene substrates such as benzene will be more favourable in this catalytic reaction.

1.2.4 Regiocontrol in C-H borylation

1.2.4.1 Steric effects in C-H borylation

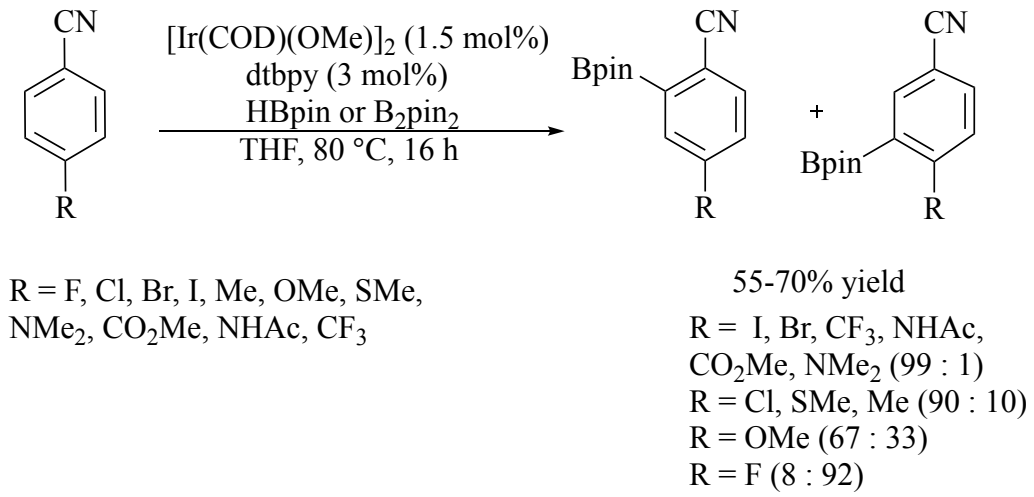
The regioselectivity in the borylation of arenes catalysed by an iridium system is predominantly controlled by steric effects. With the exception of special cases, borylation occurring at the *ortho*-position to substituents or ring junctions is sterically disfavoured. This rule in monosubstituted aromatics (Scheme 7a[10]) leads to an approximate statistical distribution of 2 : 1 for *meta*- and *para*-borylated products, with rare, or even no *ortho*-functionalized product being observed. In the borylation of symmetrically 1,2-substituted arenes (Scheme 7b[10]), steric effects lead to the formation of 4-substituted aryl boronic ester exclusively, but for 1,2-disubstituted arenes bearing two different substituents (Scheme 7c[17]), a mixture of products is obtained in most cases. Both 1,3-disubstituted (Scheme 7d[11]) or 1,2,3-trisubstituted arenes (Scheme 7e[18]) give rise to 5-substituted borylated arenes as a single product, regardless of whether the substituents of the substrates are equivalent or not. The borylation of 1,3-disubstituted

aromatics has received the greatest attention due to the ability to generate a broad range of desired 1,3,5-trisubstituted products, that are difficult to produce selectively in traditional aromatic substitution reactions.



Scheme 7 Steric effect-conducting regioselectivity for aromatic C-H borylation.[10,11,17]

Compared with 1,2 or 1,3-disubstituted arene substrates, relatively low reactivity is exhibited by 1,4-disubstituted compounds because all of the C-H bonds are sterically hindered. Borylation of unsymmetrically 1,4-substituted arenes will typically afford a mixture. However, distinct steric properties from two functionalities will make one of the possible 1,2,4-substituted arenes preferentially obtained. For instance, Smith and colleagues reported that the reactions of 4-substituted benzonitriles tended to occur *ortho* to the smaller substituents (Scheme 8).[19]

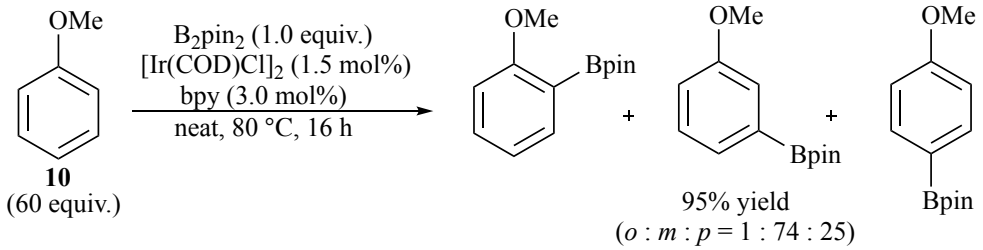


Scheme 8 Borylation of 4-substituted benzonitriles in an iridium-catalysed system.[19]

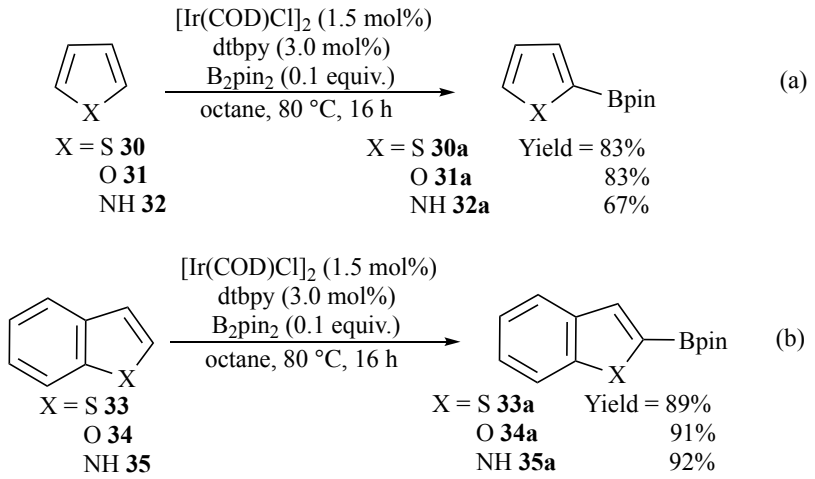
1.2.4.2 Electronic effects in C-H borylation

Electronic effects have also shown an impact upon the regioselectivity of C-H borylation. For instance, unlike reactions of many other monosubstituted benzenes which afford a statistical ratio for *meta*- and *para*-products (*ca.* 2 : 1), borylation of anisole **10** catalysed by $[Ir(COD)Cl]_2$ **14a** and bpy results in a ratio of 3 : 1 (Scheme 9),

reflecting a preference for *meta*-substitution derived from the electronic influences associated with a methoxy group.[10]



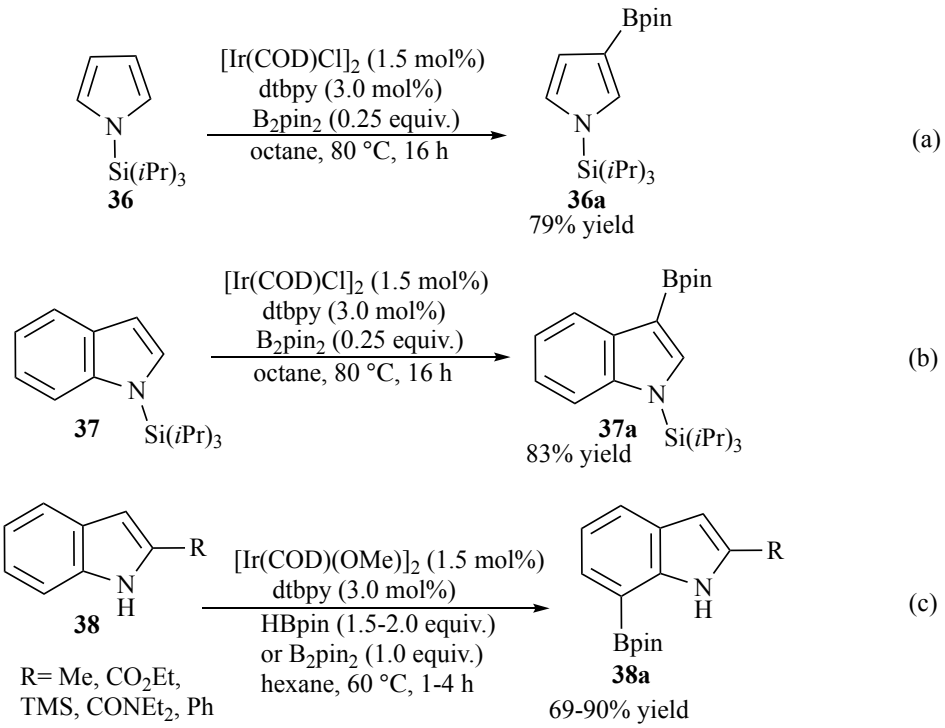
Scheme 9 Borylation of anisole catalysed by $[Ir(COD)Cl]_2$-bpy system.[10]



Scheme 10 Borylation of substrates containing five-membered heteroarenes.[20]

When there are no significant steric effects, electronic effects on C-H borylation of heteroarenes can be observed more obviously and can control the site selectivity. Early studies by Hartwig, Ishiyama, Miyaura *et al.* described the borylation of a range of heteroarenes with B_2pin_2 catalysed by $[Ir(COD)Cl]_2$-dtbpy-system.[20] Five-membered heteroarenes including thiophene **30**, furan **31**, pyrrole **32**, and their benzofused

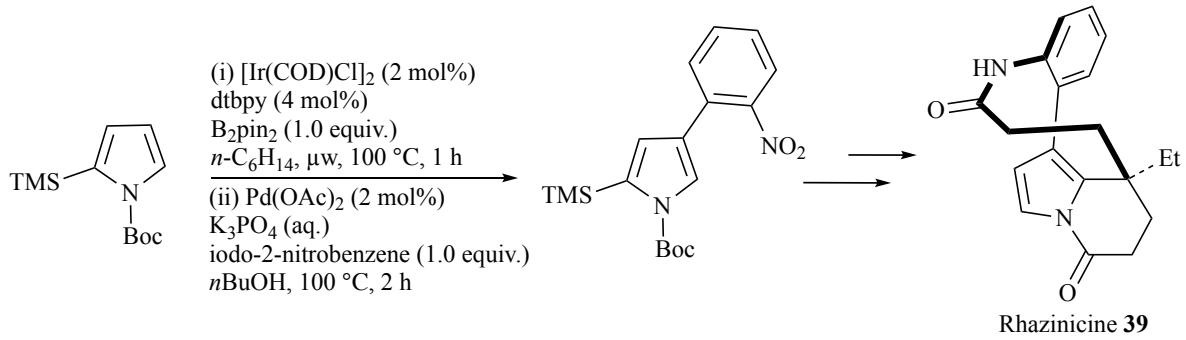
derivatives (**33**, **34**, **35**) were borylated exclusively at the 2-position in high yields (Scheme 10). This observation was consistent with computational studies which suggested that acidity was a significant factor influencing the regioselectivity of C-H activation.[21]



Scheme 11 Changes of selectivity in the borylation of pyrroles and indoles.[20,22]

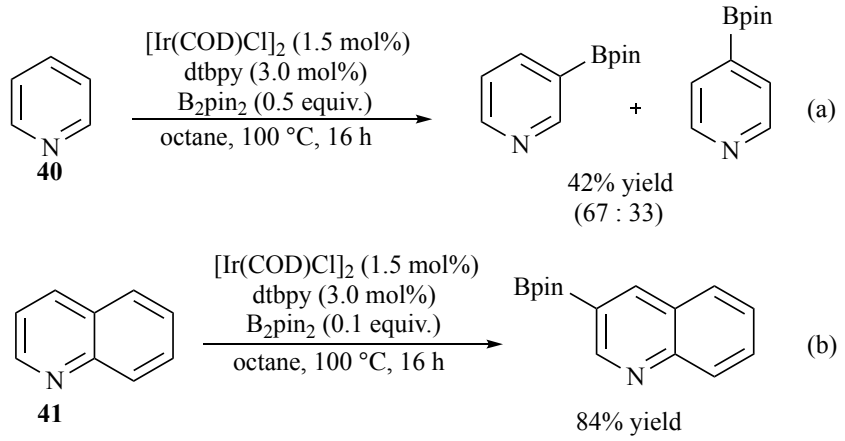
However, even in these systems steric factors can dominate. For example, regioselectivities in borylation of 5-membered heterocyclic compounds can be altered by introducing steric blocking groups on the nitrogen atom or at the *alpha*-position. Reactions of pyrroles and indoles containing a large protecting group, tri(isopropyl)silyl group, at nitrogen of the heterocycles give 3-borylated products **36a**

and **37a** (Scheme 11a and 11b).[20] Reactions of 2-substituted indoles **38** exclusively afford 7-functionalized products **38a** (Scheme 11c).[22] The strategy for using a bulky-N-protecting group to change selectivity has been applied in versatile methodologies to prepare natural products and pharmaceutical drugs. For example, Guant *et al.* reported a total synthesis of rhazinicine **39**, which involved the borylation of N-Boc protected pyrrole derivatives selectively at the 3-position as a key step (Scheme 12).[23]



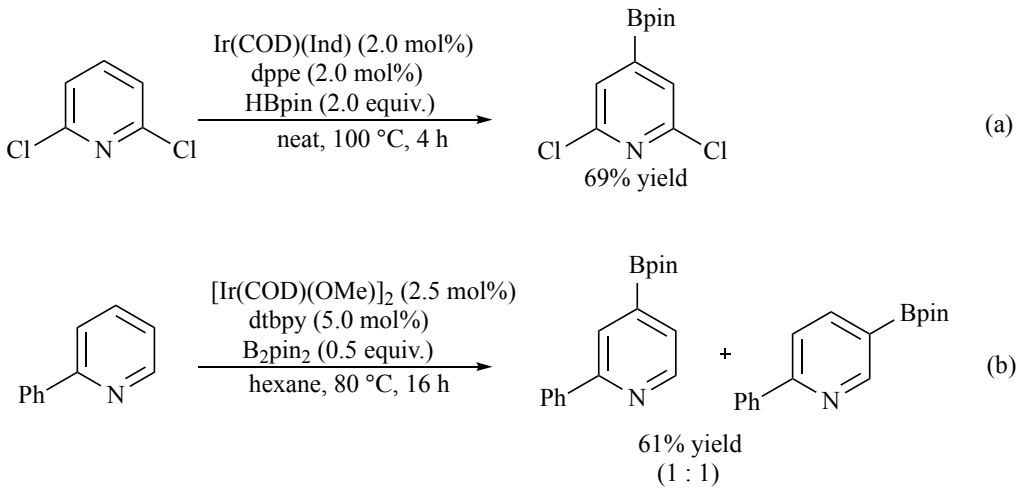
Scheme 12 A total synthesis of rhazinicine **39** by Guant *et al.*[23]

Borylation of substrates containing 6-membered rings is controlled by electronic factors in a different way. Unsubstituted pyridine **40** gives an approximate statistical distribution of 2 : 1 for *meta*- and *para*-borylated products (Scheme 13a[24]), whereas quinoline **41** selectively affords 3-borylated products (Scheme 13b[20]). The poor reactivity of pyridine in borylation can be attributed to the coordination between the basic nitrogen atom and the iridium catalyst that inhibits a significant quantity of the active catalyst.[24] The higher efficiency of quinoline is proposed to be due to the steric effect from the benzofused ring preventing the coordination between iridium complex and substrate.

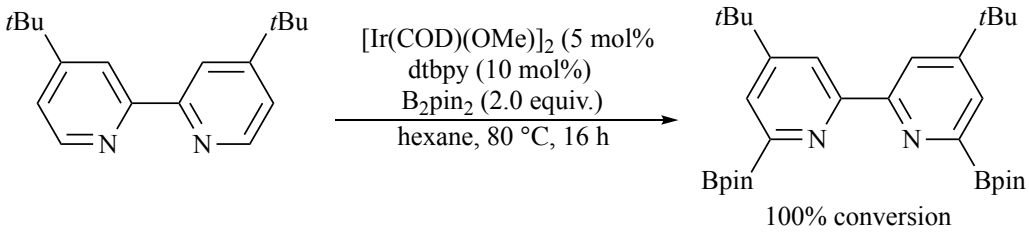


Scheme 13 Borylation of pyridine **40** and quinoline **41**.[20,24]

Difficulties arising from the pyridyl coordination can be reduced by the incorporation of *ortho*-substituents. Borylation of 2,6-disubstituted pyridines gives much higher efficiency compared with that of unsubstituted pyridine. Steric hindrance of the 3-position allows the functionality to be exclusively installed at the 4-position (Scheme 14a[9]), analogous to the reaction of 1,3-disubstituted arenes. Pyridines bearing one substituent at the 2-position react to form 4- and 5-borylpyridines, with the sterically accessible 6-position remaining unreactive (Scheme 14b[25]).

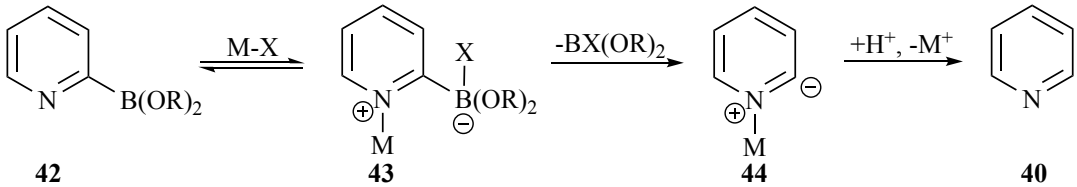


Scheme 14 Borylation of pyridines containing *ortho*-substituents.[9,25]



Scheme 15 Borylation of dtbpy **16c**.[25]

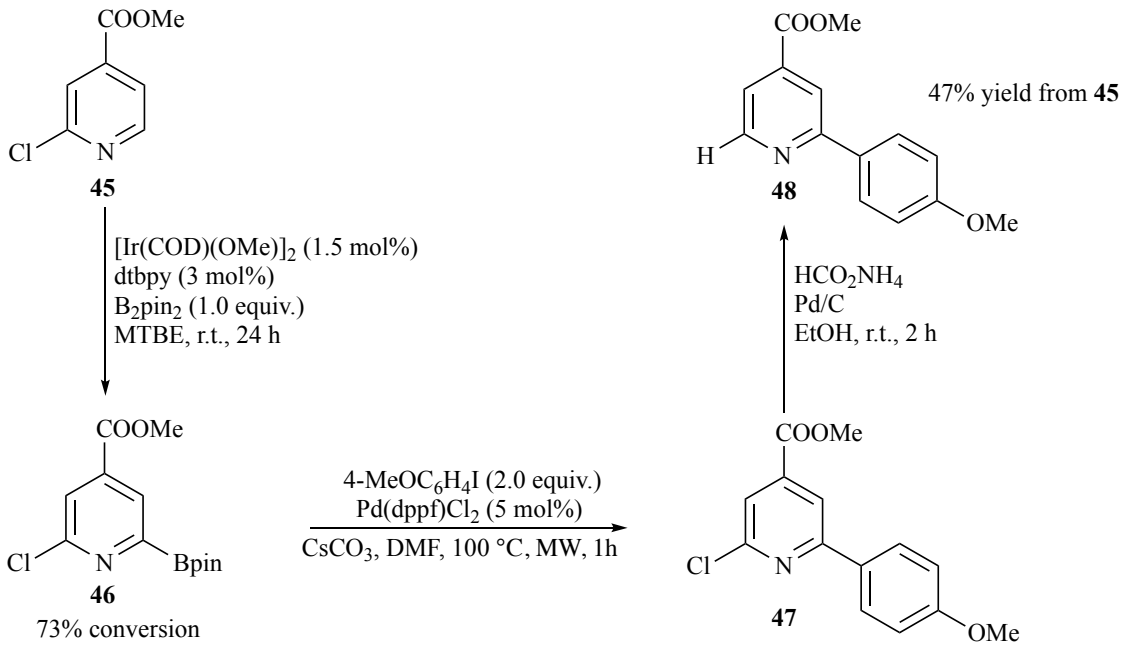
The challenge of borylation adjacent to the pyridyl nitrogen has been attributed to the electronic repulsion between the nitrogen lone pair and the partial negative charge on the C-2 during the C-H activation process.[26] This electronic effect can be overcome when reactions at other positions are sterically inhibited, as is shown in the borylation of dtbpy **16c** which is forced to afford 2-borylated product (Scheme 15).[25]



Scheme 16 Proposed mechanism for protodeboronation of 2-borylated pyridines.[27]

However, even in this case, the α-pyridyl boronic esters are prone to undergo rapid protodeboronation, making access to these reagents challenging.[26,28–30] The mechanism of protodeboronation has not been well-established. Kuivila and colleagues[31,32] have suggested that this decomposition may be catalysed by acids, bases, or metal salts. One scenario suggested by Stevens[27] is that after the protonation of the nitrogen atom, the

resulting zwitterion **43** undergoes nucleophilic substitution of the boryl group to form the ylide intermediate **44**, which then reproduces the parent pyridine **40** *via* rapid electron rearrangement (Scheme 16). As such, in a similar version to that described above, this protodeboronation process can be minimized by lowering the basicity of the pyridyl nitrogen with a sufficiently electronegative *o*-substituent. This has been exemplified by the borylation of methyl 2-chloroisonicotinate **45**, which gives a stable α-pyridyl boronic ester **46** that readily undergoes subsequent functionalization (Scheme 17).[26]

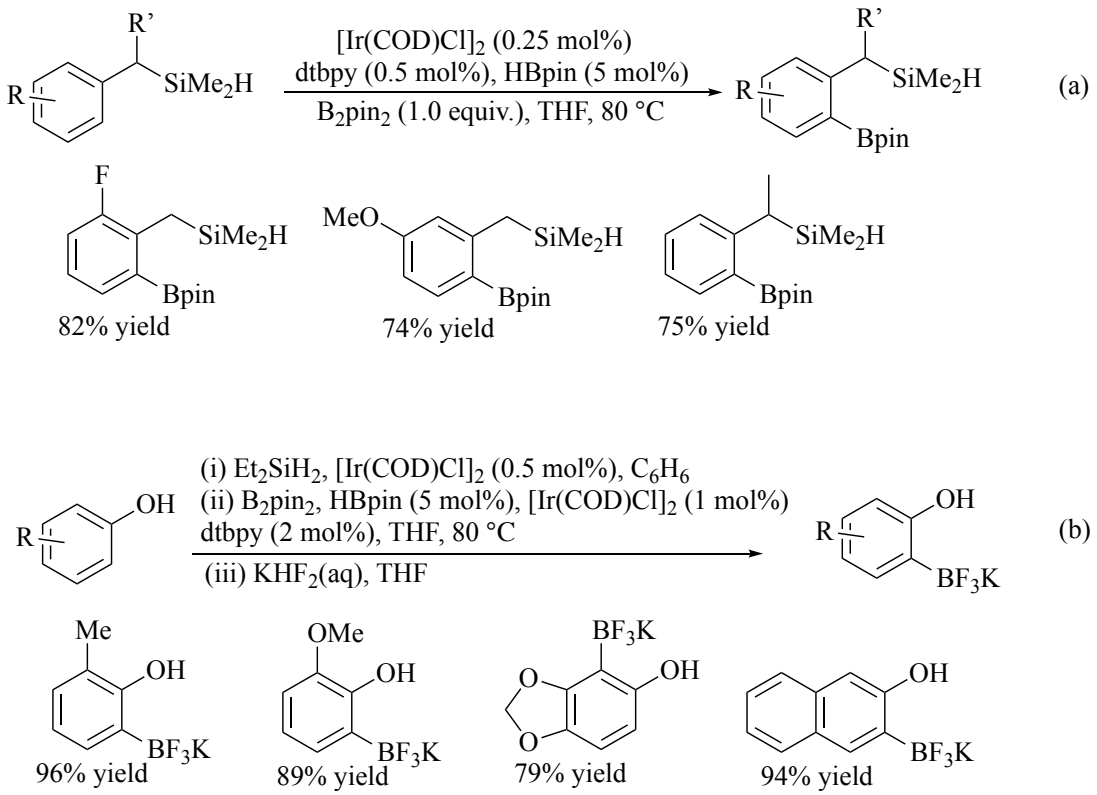


Scheme 17 Reaction sequences containing stable α-pyridyl boronic ester.[26]

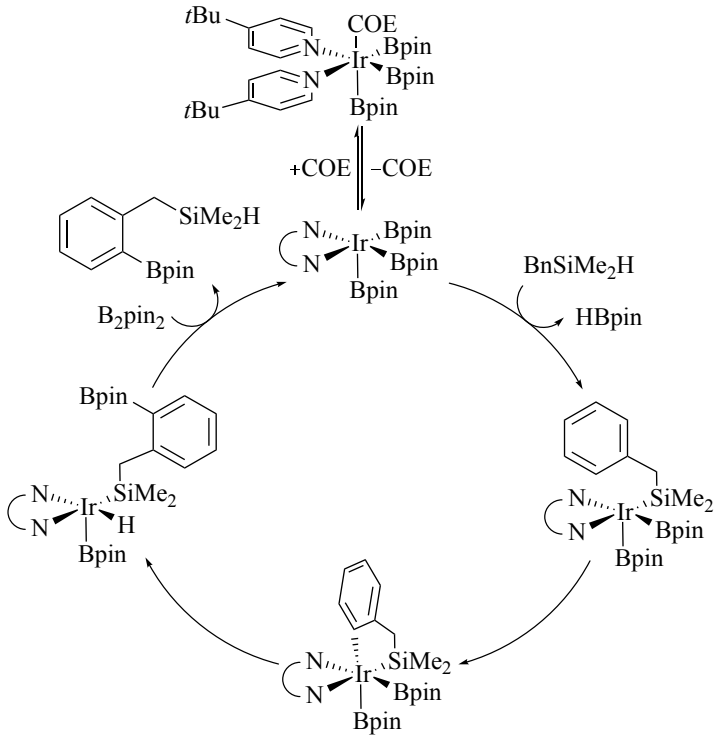
1.2.4.3 Directed *ortho*-borylation

The regioselectivity controlled by steric effects in arene borylation often complements

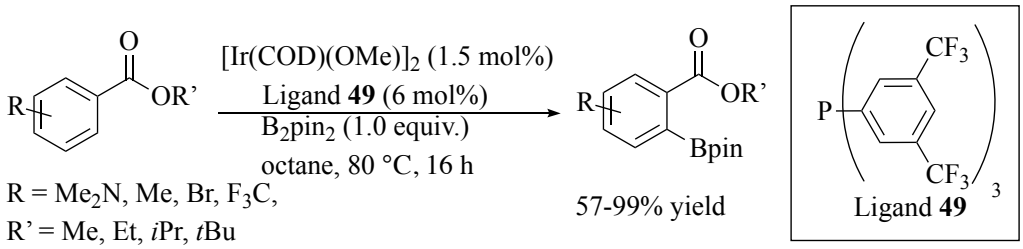
that of electrophilic aromatic substitution or directed *ortho* metalation (D*o*M).[33] However, a mild alternative to conduct directed borylation would be valuable. Hartwig and Boebel reported a silyl-directed arene borylation catalysed with $[Ir(COD)Cl]_2$-dtbpy-system.[34] In this method, the introduction of a hydrosilyl group as a directing group leads to benzyls and phenols facilitating exclusively *ortho*-borylation (Scheme 18). Reversible addition of an Si-H bond of the hydrosilyl group to the metal centre was proposed to account for the mechanism of this reaction (Scheme 19). This docking of the arene substrate at the catalyst through the silicon atom makes borylation occur preferentially at the position *ortho* to the substituent.



Scheme 18 *ortho*-Directed arene borylation developed by Hartwig and Boebel.[34]



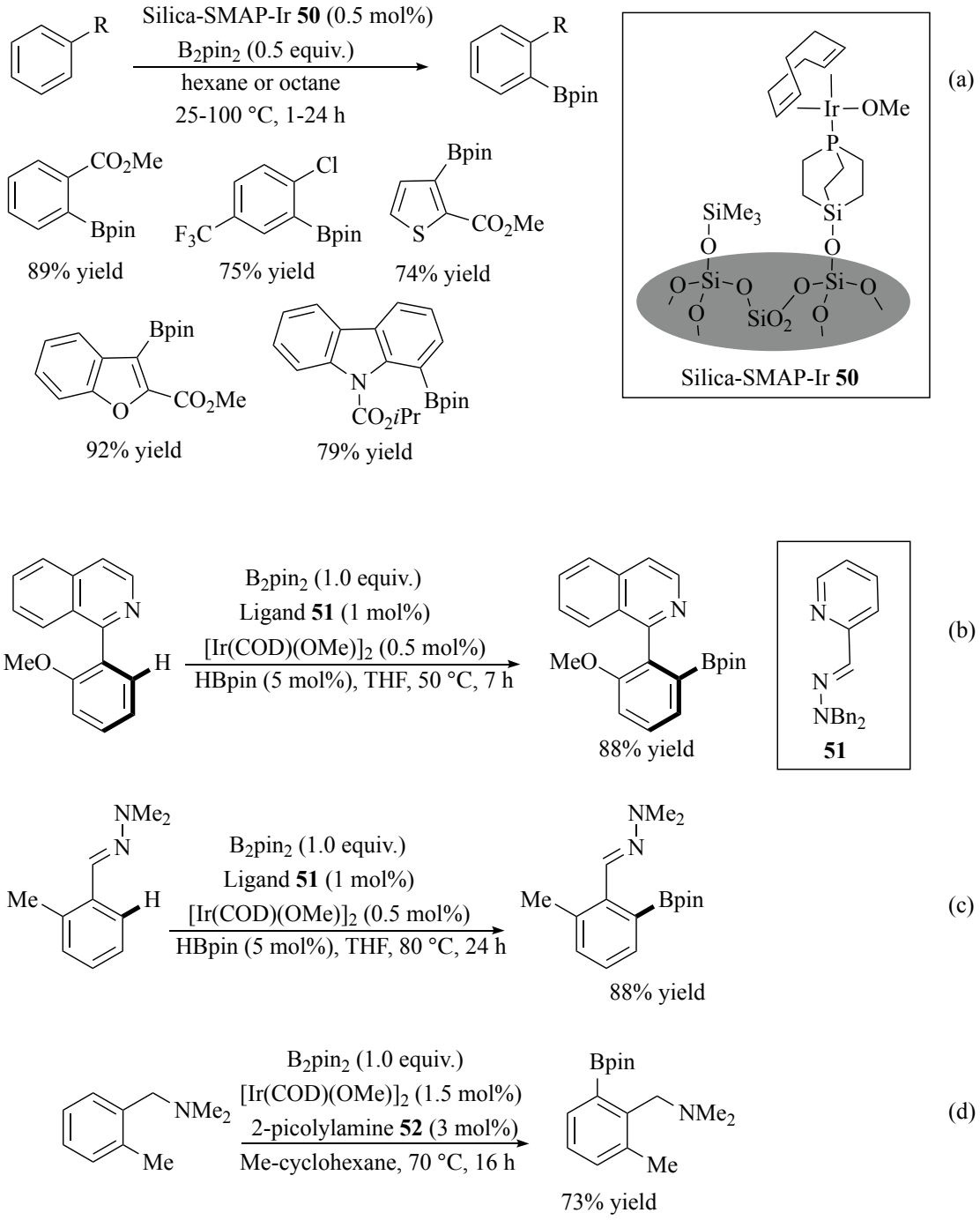
Scheme 19 Mechanism for hydrosilyl-directed *ortho*-borylation of arenes.[34]



Scheme 20 *ortho*-Directed borylation of benzoates.[35]

Ishiyama, Miyaura *et al*. demonstrated the *ortho*-directing effect of a catalyst system consisting of $[Ir(COD)(OMe)]_2$ and an electron-deficient monodentate phosphine ligand **49**, which can borylate benzoates to generate selective products in moderate to excellent yields (Scheme 20).[35] This methodology is dependent on chelation control,

by which coordination of the ester functionality to the metal centre allows the subsequent cleavage of an *ortho* C-H bond. Ishiyama and Miyaura then extended the substrate scope of this protocol to aryl ketones.[36]



Scheme 21 Selected examples of developments of *ortho*-directed C-H borylation.[37–39]

Sawamura and colleagues described the first examples of the solid-supported catalyst, Silica-SMAP-Ir **50**, in arene borylation (Scheme 21a).[37] This methodology has also been applied to the *ortho*-borylation of heteroarenes[40] and phenol derivatives.[41] Fernandez and Lassaletta performed the Ir-catalysed nitrogen-directed *ortho*-borylation on 2-aryl pyridine and aromatic *N,N*-dimethylhyarazone substrates under mild conditions using a hemilabile *N,N*-ligand **51** (Scheme 21b and 21c).[38] Recently, in related work, Clark and colleagues reported the *ortho*-borylation of benzylic amines using 2-picolylamine **52** as a ligand (Scheme 21d).[39]

1.2.4.4 Directed *meta*-borylation

In 2015, Kuninobu, Kanai and co-workers developed the first Ir-catalysed *meta*-selective C-H borylation of α-aryl carbonyl compounds using well-designed catalytic system.[42] In this method, the bipyridine ligand that binds to the metal centre contains a pendant urea moiety (Figure 2). The secondary interaction between this urea moiety and the carbonyl group controls the regioselectivity by placing the iridium centre in the vicinity of the *meta*-C–H bond.

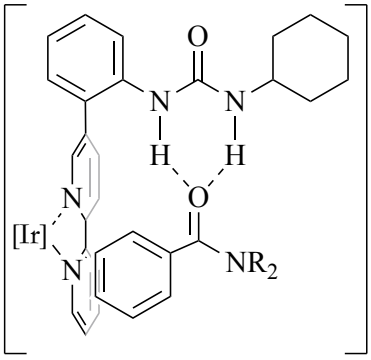


Figure 2 Secondary interaction between the ligand and substrate.[42]

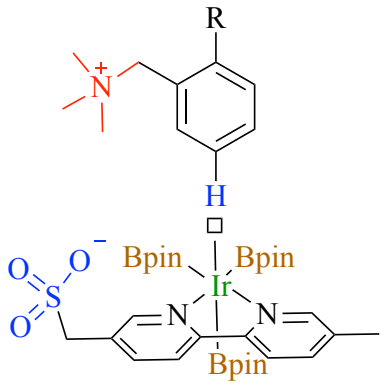


Figure 3 Noncovalent interaction between cationic substrate and anionic ligand.[43]

In 2016, Phipps *et al.* reported an alternative strategy for *meta*-borylation, in which an ion pair interaction was introduced between quaternary ammonium salts in the arene substrates and the anionic ligand to achieve the desired regioselectivity (Figure 3).[43]

1.2.4.5 Directed *para*-borylation

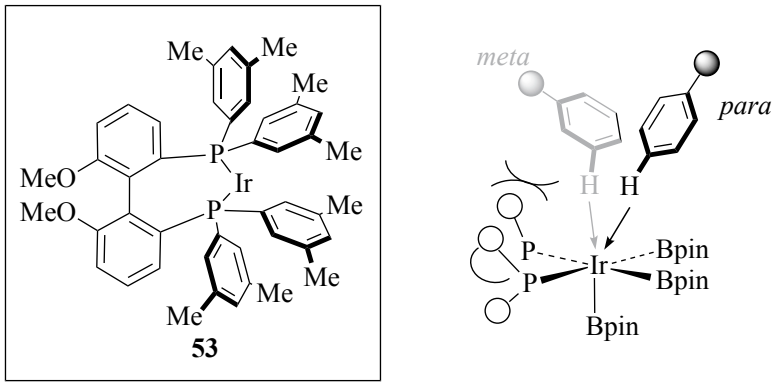


Figure 4 *Para*-selective borylation directed by bulky ligand.[44]

Recently, Itami and co-workers developed a method for highly *para*-selective aromatic

C-H borylation.[44] By using a novel catalyst with bulky phosphine ligand **53**, the monosubstituted benzenes can be directed to *para*-borylation with up to 91% yield (Figure 4). Higher yields can be achieved by increasing the bulkiness of the substituent, demonstrating the crucial role that steric repulsion between substrate and catalyst plays in regiocontrol of C-H borylation.

1.2.5 Conclusions

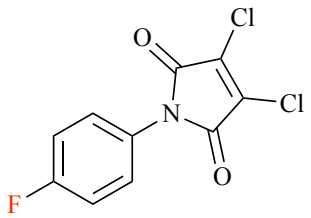
In summary, as is shown in the above examples, since the first observation of iridium-catalysed aromatic C-H borylation in 1999, numerous improvements in this field have been made. Ligand screening provided the reaction system with high efficiency and practical protocol, successfully conducting the reaction at room temperature to give large turnovers and excellent yields. Substrate scope has been expanded from benzene to a wide range of functionalized arenes and heteroarenes. Mechanistic studies of the most active Ir-dtbpy-system suggests that the pathway involves the reductive elimination of the borylated arene, the ensuing oxidative addition of B_2pin_2, and the reductive elimination of HBpin to regenerate the active Ir(III) complex. Whilst the regioselectivity of C-H borylation is governed by steric factors, the inherent electronic effects that direct the C-H activation to the most acidic position should not be neglected.

1.3 Fluoroaromatics

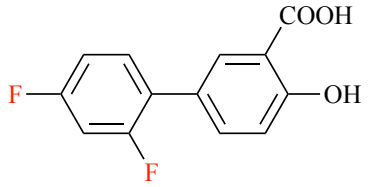
1.3.1 Fluoroarenes

The wide introduction of fluorinated substituents into organic aromatic molecules leads

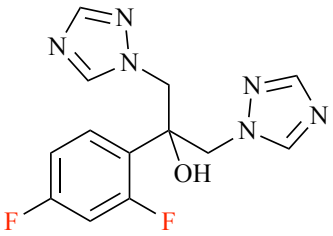
to significant changes in their chemical reactivity, physical properties, and physiological activity. Fluoroarenes have been broadly employed in many fields, ranging from solvents and catalysts to pharmaceutical drugs and agrochemicals.[45] At present, an estimated 30% of agrochemicals and 20-25% of pharmaceuticals contain fluorine atoms (Figure 5).[45–47] These fluoroaromatic moieties were introduced to modify the lipophilicity, bioavailability, acidity and more importantly, the metabolic stability of the drugs.[46]



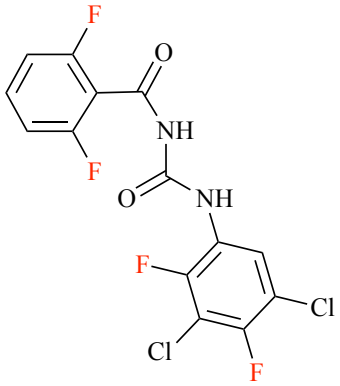
Fluoroimide: a fungicide



Diflunsial: an analegic; antiinflammatory



Fluconazole: an antifungal drug



Teflubenzuron: an insecticide

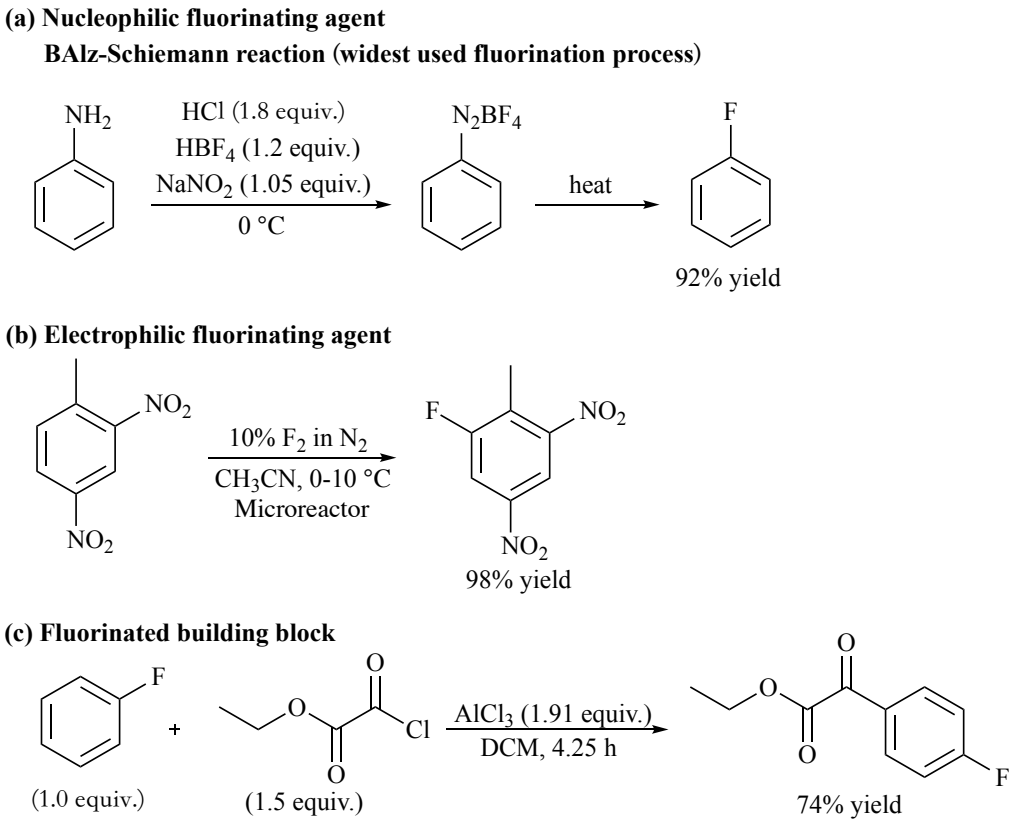
Figure 5 Examples of pharmaceutically and agriculturally important fluoroarenes[45–47]

Although organofluorine compounds are in great demand by mankind, fluorine mainly occurs in inorganic materials in nature whereas naturally occurring organofluorine compounds have rarely been identified. Therefore, all of the fluorinated aromatic compounds used in these applications must be artificially synthesised and it is

worthwhile to develop practicable and efficient synthetic routes to them.

1.3.2 Synthesis of fluoroarenes

To date, numerous conventional synthetic methods for fluorinated aromatics have been well-established, either using direct fluorination with fluorinating reagents (Scheme 22a[48] and 22b[49]) or by synthesising them from fluorinated building blocks (Scheme 22c[50]).



Scheme 22 Methods for preparation of fluoroarenes.[48–50]

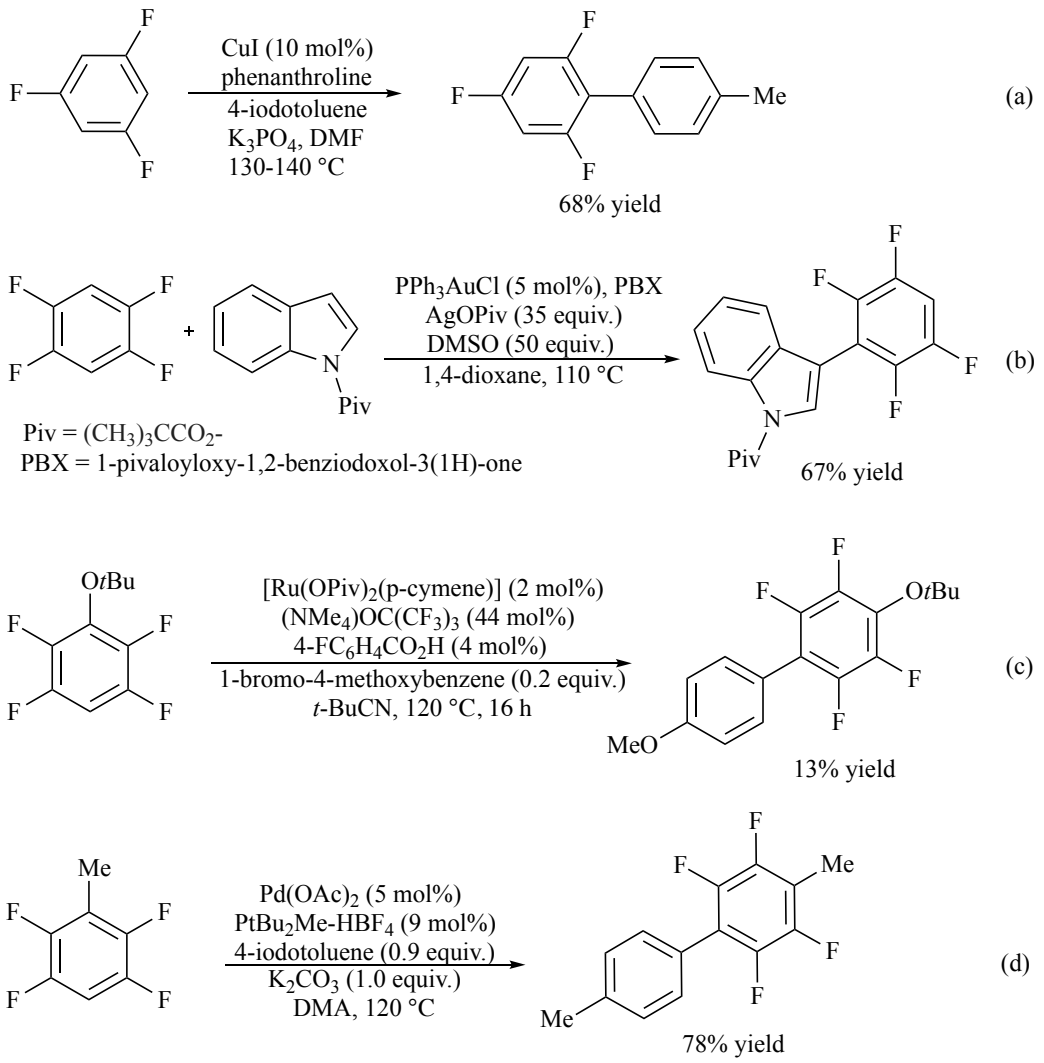
These established fluorination procedures can be used on industrial scales; however, applications are limited in the synthetic chemistry due to the harsh conditions and specialised equipment required. In recent years, strategies for the late-stage

introduction of fluorine atoms have been developed, which can reduce the loss of fluorine-containing intermediates in side reactions or purification. However, it is still challenging to control regio-, chemo- and stereoselectivity in the construction of C-F bonds. As a result, the use of fluorinated building blocks to generate target molecules is more practicable and wide spread in modern fluorine chemistry.

1.3.3 C-H activation of fluoroarenes

In terms of atom utilization and reaction efficiency, C-H activation/functionalization is the most straightforward way to prepare target fluorinated aromatic molecules. Over recent decades, methodologies for direct C-H arylation of fluorinated arenes mediated by Cu (Scheme 23a),[51,52] Au (Scheme 23b),[53,54] Ru (Scheme 23c),[55] and Pd-based catalysts (Scheme 23d),[56–58] have been developed. Studies of challenging regioselectivity issues have been reported. For example, Fagnou *et al*.[56] disclosed that the preference of direct arylation *ortho* to the fluorine substituents using palladium catalysts resulted from the acidities of C-H bonds in these positions. Larrosa's group[57] reported another breakthrough in selective C-H arylation, performing the first examples of Pd-catalysed *meta*-C-H functionalization of fluoroarenes using CO_2 as a transient directing group.

However, for these reactions, inherent challenges arising from the requirement of harsh reaction conditions, often associated with poor functional group tolerance and limited substrate scope, remain unsolved.

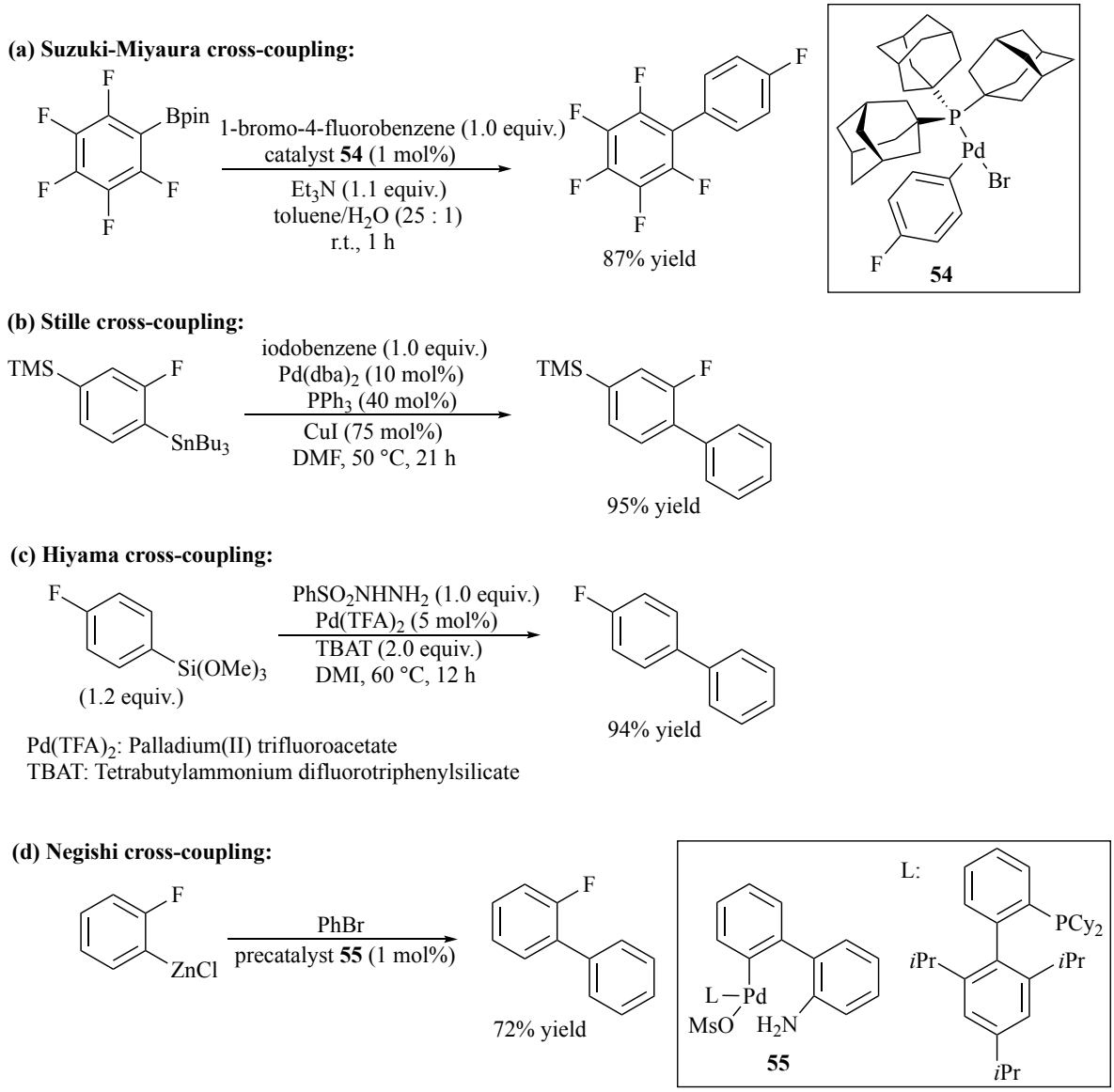


Scheme 23 Preparation of fluoroarenes using transition metal-catalysed C-H arylation.[51,54–56]

1.3.4 Ar^F-M cross-coupling chemistry

Compared to the direct C-H arylation strategy discussed above, transition metal catalysed cross-coupling reactions of fluoroaryl organometallics can be used to synthesise fluorinated aromatics under milder conditions. For example, transformations of suitable fluorinated aromatic precursors under Suzuki-Miyaura (Scheme 24a),[59] Stille (Scheme 24b),[60] Hiyama (Scheme 24c),[61] and Negishi coupling conditions

(Scheme 24d)[62] have been reported. Of these various cross-coupling approaches the use of fluorinated aryl boronic esters represents a powerful synthetic method to avoid difficulties in the late stage incorporation of fluorine atoms. This method has the advantages of wide substrate scope, reduced toxicity when compared to using organostannane and organozinc compounds, and low cost of reagents. Therefore, access to readily accessible fluorinated boronic ester derivatives is currently of high interest for synthetic chemists.

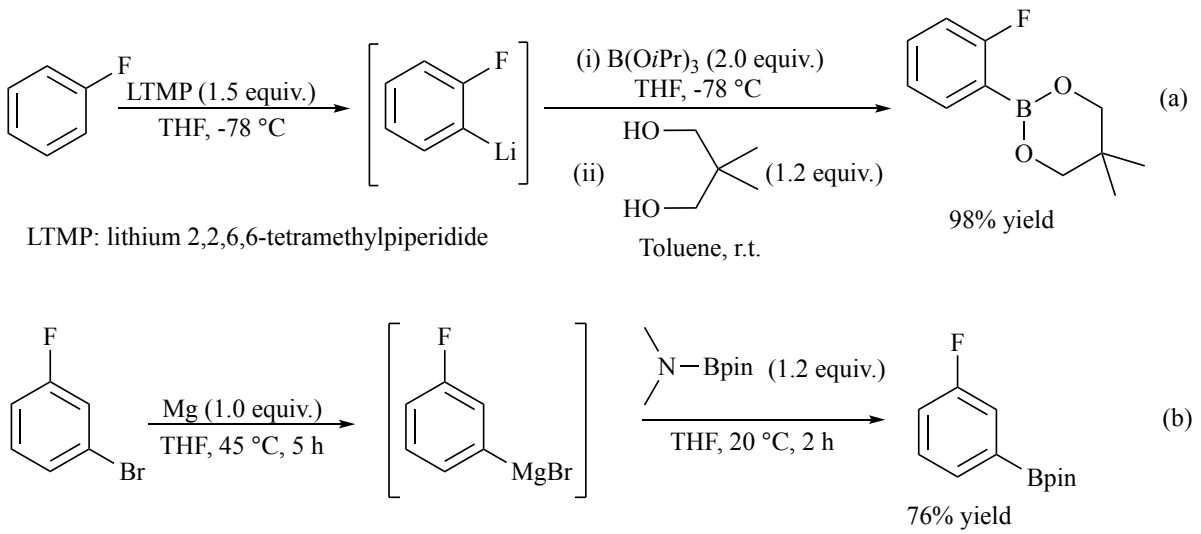


Scheme 24 Cross-coupling reactions of fluorinated arene precursors.[59–62]

1.3.5 Synthesis of fluorinated aryl boronic esters

1.3.5.1 Electrophilic borate trapping of arylmetal intermediates

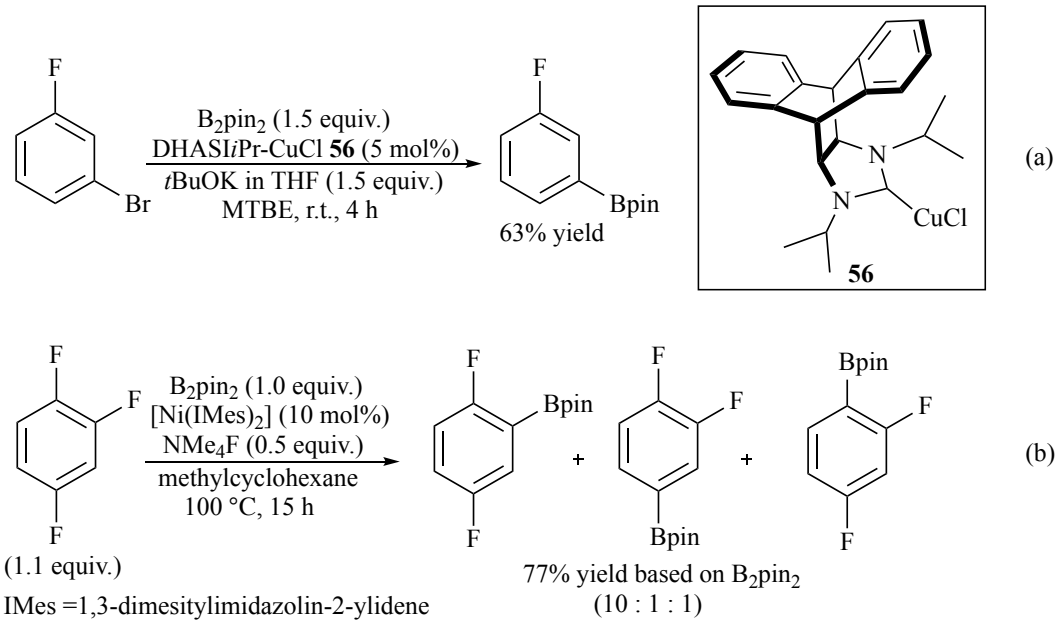
Strategies for fluorinating aryl boronic esters remain unknown. In contrast, there are several methods in which boronate substituents can be installed onto fluorinated aromatic rings. A traditional process for the preparation of fluorinated boronic esters begins with the generation of an organometallic compound by either metalation of an arene (Scheme 25a[63]) or metal-halogen exchange with an aryl halide (Scheme 25b[64]), followed by trapping the arylmetal intermediate with a borate, before an acid hydrolysis to release the product. Despite moderate to good yields of borylated products, such routes are limited by the low functional group compatibility of these hard-organometallic compounds and the requirement for low temperature conditions.



Scheme 25 Preparation of fluorinated boronic esters from Grignard or ArLi reagents.[63,64]

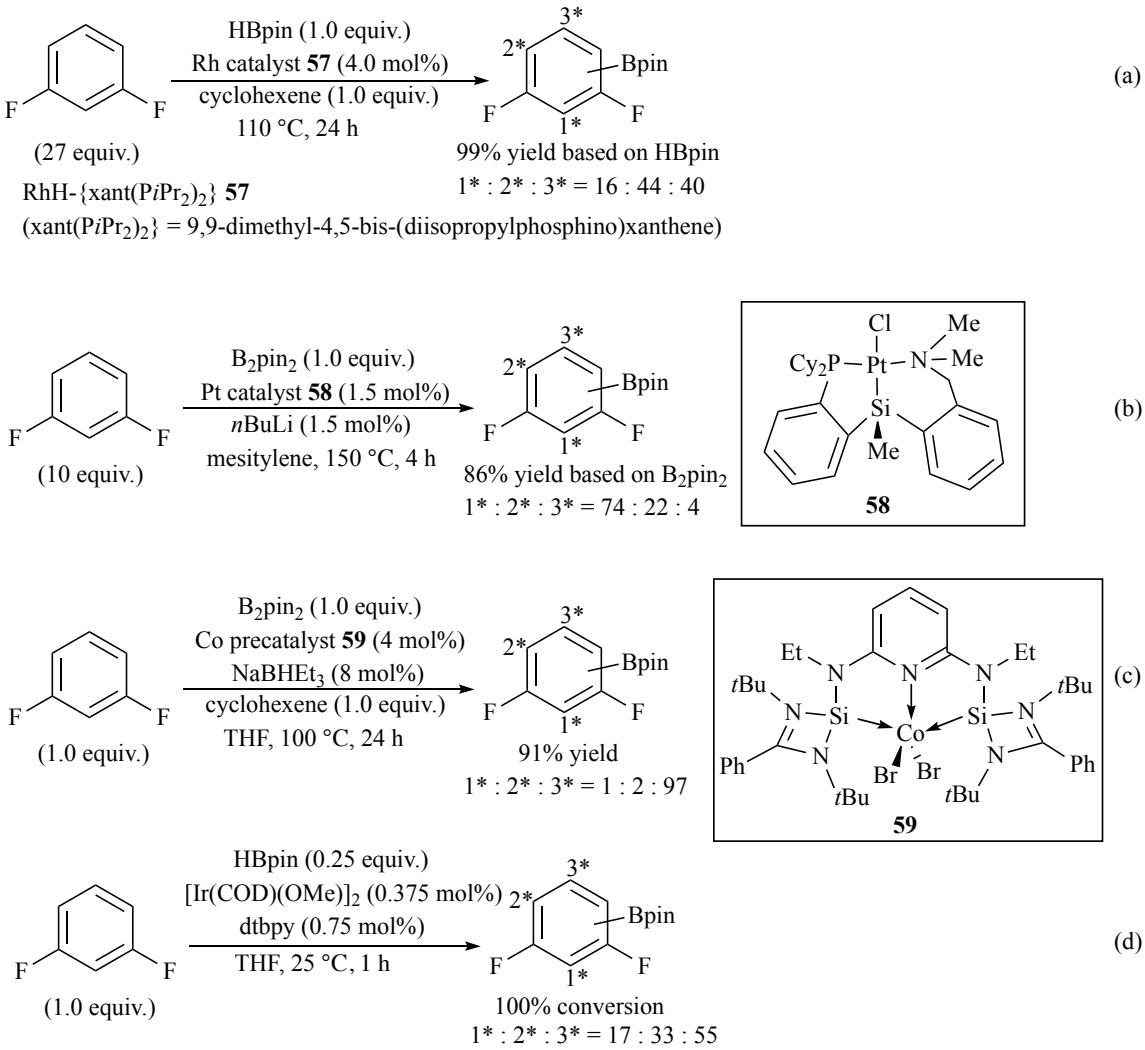
1.3.5.2 C-X borylation of aryl halides

Direct catalytic borylation of an aryl C-X (X = Cl, Br, I) bond using a transition metal can represent a milder technique to synthesise the required boronic esters (Scheme 26a[65]). However, access to suitable halogenated substrates with regioselective installation of halogen atoms are prohibitively challenging owing to the strong electron-withdrawing nature of the fluorine substituents, which decreases the nucleophilic character of the aromatic ring and interferes with the electrophilic functionalization process. Recently, a protocol involving nickel-catalysed C-F borylation of fluoroaromatic compounds has emerged (Scheme 26b).[66] However, non-symmetrical substrates can lead to a mixture of isomeric products and the issue of regioselectivity remains an unsolved challenge.



Scheme 26 Preparation of fluorinated boronic esters *via* C-X borylation.[65,66]

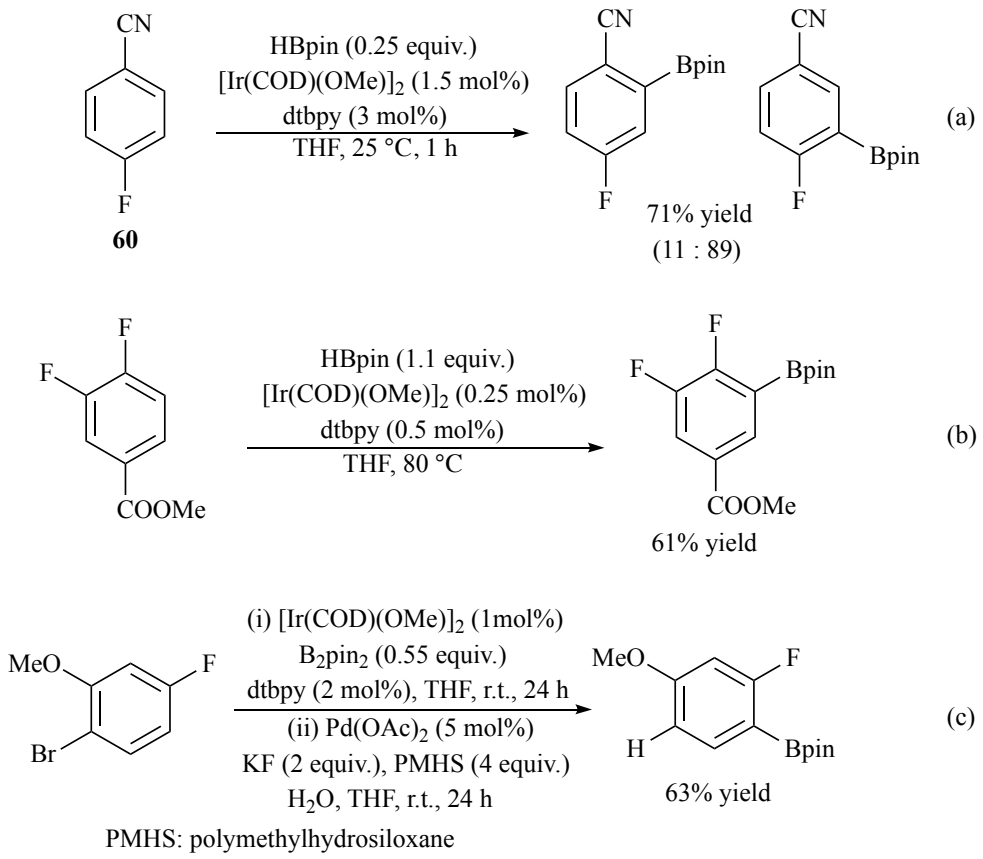
1.3.5.3 Direct C-H borylation of fluoroarenes



Scheme 27 C-H borylation of 1,3-difluorobenzene using different metal catalysts.

More recently, a more attractive and versatile approach to access aryl boronic esters is the transition metal mediated C-H activation of fluoroarenes. This obviates the need for cryogenic conditions, strong bases, and the prior preparation of haloaromatic precursors. A variety of metal complexes have been reported for this transformation, including POP-supported rhodium catalysts (Scheme 27a),[67] PSiN-pincer platinum catalysts

(Scheme 27b),[68] cobalt(II) bis(silylene)-based precatalysts (Scheme 27c)[69] and the iridium bipyridine-based catalysts that were discussed previously (Scheme 27d).[19]



Scheme 28 Selected examples of Ir-catalysed borylation of fluorinated arenes.[19,70,71]

Several research groups have explored the scope of iridium catalyst-mediated fluoroarene borylation. Smith and co-workers performed the borylation of 4-fluorobenzonitrile **60**, for which the regioselectivity outcome arises from both the small steric hindrance and the *ortho*-directing effect of the fluorine atom (Scheme 28a).[19] Hartwig and Robbins demonstrated the sterically controlled regioselectivity of the

borylation of trisubstituted fluoroarenes, in which functionalization occurs *ortho* to fluorine to minimize repulsion with other functional groups (Scheme 28b).[70] Oppenheimer, Smith and Maleczka *et al*. developed a two-step borylation/dehalogenation reaction sequence where bromine or chlorine atoms serve as blocking groups to increase the selectivity for *ortho*-fluorinated borylated products (Scheme 28c).[71] While these are important progresses, to date, no general study that extensively explores the Ir-catalysed borylation of different polyfluorinated substrates has been reported. Additionally, the subtle balance between steric and electronic influences of fluorine substituents are incompletely known.

1.3.6 Conclusions

As discussed in the previous sections, fluorinated boronic esters are a range of versatile precursors for the preparation of substituted fluoroaromatics. Several synthetic routes have been developed for the preparation of these fluorinated reagents, including electrophilic borate trapping of arylmetal intermediates, C-X borylation of aryl halides, and direct C-H borylation of fluoroarenes. Among these methods, Ir-catalysed C-H borylation of suitable fluoroarenes is currently the most attractive one because it obviates the requirements for strong bases, low temperature conditions, and the pre-generation of haloaromatic precursors. However, the substrate scope, particularly for polyfluorinated arenes substrates, has not been fully studied.

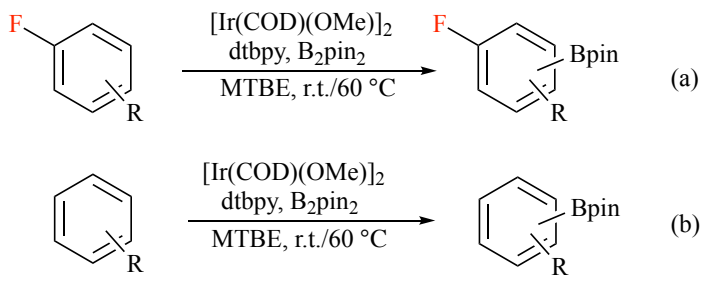
1.4 Aims of this project

The high efficiency and predictable regioselectivity of iridium-catalysed C-H borylation reactions have made them very useful transformations in the synthesis of fluorinated building blocks. While the regioselectivity in Ir-catalysed aryl C-H borylation is recognised to be driven by steric effects which make *meta*- or *para*-functionalization more favourable, it is possible to install the Bpin group *ortho* to the small fluorine atom when compared with other aryl functionalities. Moreover, it is well-established through both thermodynamic[72] and kinetic studies[73] that the more acidic C-H bonds *ortho* to fluorine atoms can be preferentially activated by transition metal catalysts. As such, C-H borylation reactions of fluorinated arene substrates with more than one sterically available C-H bond represent an unexplored area for the synthesis of fluorinated aryl boronic esters. The selectivity and effectiveness of this process remain to be determined and the aim of this project was to address this issue through Ir-catalysed C-H borylation of a series of polyfluorinated arenes.

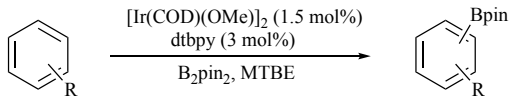
2.0 Results and discussion

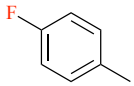
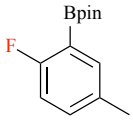
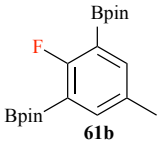
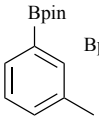
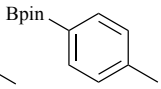
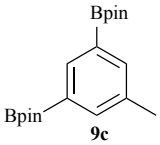
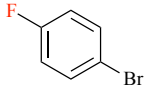
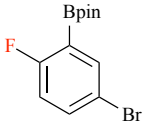
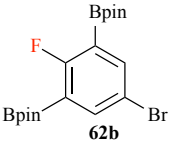
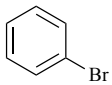
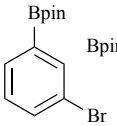
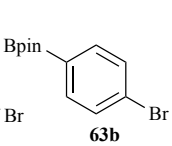
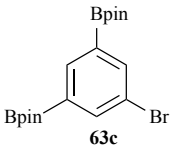
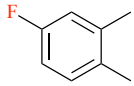
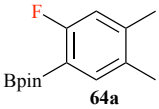
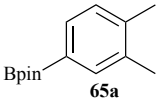
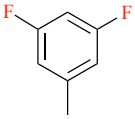
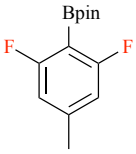
2.1 Borylation of simple fluoroarenes

As discussed in Chapter 1, the reported examples of borylation *ortho* to a C-F bond in early studies have demonstrated that the steric hindrance of a fluorine atom can be overridden when there are no other sterically available positions. However, these reactions were generally conducted at elevated temperatures and were not conducive to high selectivity. As a means of verifying this sterically controlled *o*-borylation at room temperature, gaining preliminary assessment of the applicability of this Ir-catalysed C-H borylation methodology to fluoroarenes, and gaining experience in carrying out the procedure, it was decided to carry out the comparative experiments shown in Scheme 29.



Scheme 29 Ir-catalysed C-H borylation of fluoroarenes and parent arenes at room temperature/60 ℃.



Entry	Substrate	Products	Condition	Conv./%	Ratio	Yield%
1 2	 **61**	 **61a**  **61b**	ad bd	88 (16 h)[f] 83 (24 h)[f]	4 : 1 6 : 1	— 18 (**61a**)
3	 **9**	 **9a**  **9b**  **9c**	ad	30 (16 h)[g]	63 : 31 : 6	—
4 5	 **62**	 **62a**  **62b**	cd ae	82 (4 h)[f] 95 (17 h)[f]	4 : 1 1 : 47	14 (**62a**) 61 (**62b**)
6	 **63**	 **63a**  **63b**  **63c**	cd	65 (4 h)[g]	67 : 19 : 14	—
7 8	 **64**	 **64a**	ad ae	58 (18 h), 83 (44 h)[f] 98 (1 h)[f]	— —	— 65
9 10	 **65**	 **65a**	ad ae	36 (18 h), 54 (44 h)[g] 50 (1 h)[g]	— —	— —
11	 **66**	 **66a**	ad	57 (1 h), 90 (3 h)[f]	—	71

(a) 1.2 equiv. of B_2pin_2 was used; (b) 1.0 equiv. of B_2pin_2 was used; (c) 0.6 equiv. of B_2pin_2 was used; (d) performed at room temperature; (e) performed at 60 °C; (f) Conversion was based on arene substrate and detected by ^{19}F NMR spectroscopy; (g) Conversion was based on arene substrate and detected by GC-MS.

Table 5 Fluorine-assisted *ortho*-borylation to a C-F bond.

Previous work in the group has demonstrated the effectiveness of methyl *tert*-butyl ether (MTBE) as a C-H borylation solvent.[74] Based on this and a literature procedure,[10] borylation of a group of fluorinated arenes and their corresponding parent arenes were

conducted with an excess of boron source to drive the reaction to completion. For example, charging a Schlenk tube with a combination of $[Ir(COD)(OMe)]_2$ (1.5 mol%), dtbpy (3.0 mol%), and B_2pin_2 (1.2 equiv.), followed by flushing the mixture with nitrogen and the addition of anhydrous MTBE, gave the black active catalyst species. The substrate, **61** or **9**, was then added. The mixture was stirred at room temperature before being monitored by ^{19}F NMR or GC-MS. The resulting fluorinated aryl boronic esters were isolated by flash column chromatography and characterised by NMR analysis.

For fluoroarene **61** (Table 5, entry 2), mono- and bis-borylated products were firstly identified based on the degree of downfield shift of the fluorine signal (approximately 10 ppm) that is typical for an *o*-borylated C-F bond and GC-MS trace (M^+ peaks of 236 and 362 m/z), and were further confirmed by an NMR analysis of the isolated products (*vide infra*). Due to the possible decomposition of products during GC analysis, the ratio between two products and the conversion of **61** were calculated by integrations of the fluorine peaks in the ^{19}F NMR spectrum of the crude mixture (Figure 6). The ratio of the two signals at -108.4 and -97.5 ppm indicated an approximate 6 : 1 ratio of mono- and bis-borylated products and comparison of the integrated areas of the substrate peak (-118.7 ppm) to the total integration showed an 83% conversion of **61**. The crude mixture was then subjected to flash column chromatography to afford 18% of **61a**, which was fully characterised by ^{1}H, ^{13}C, ^{19}F, and ^{11}B NMR techniques.

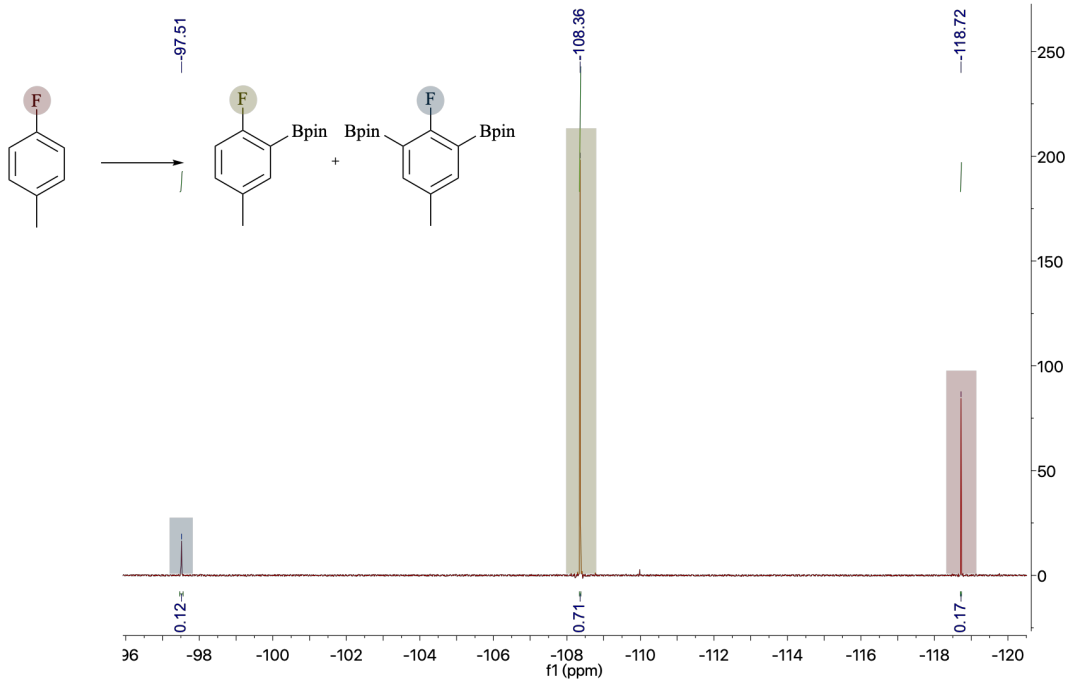


Figure 6 ^{19}F NMR spectrum of the crude mixture of borylation of **61**.

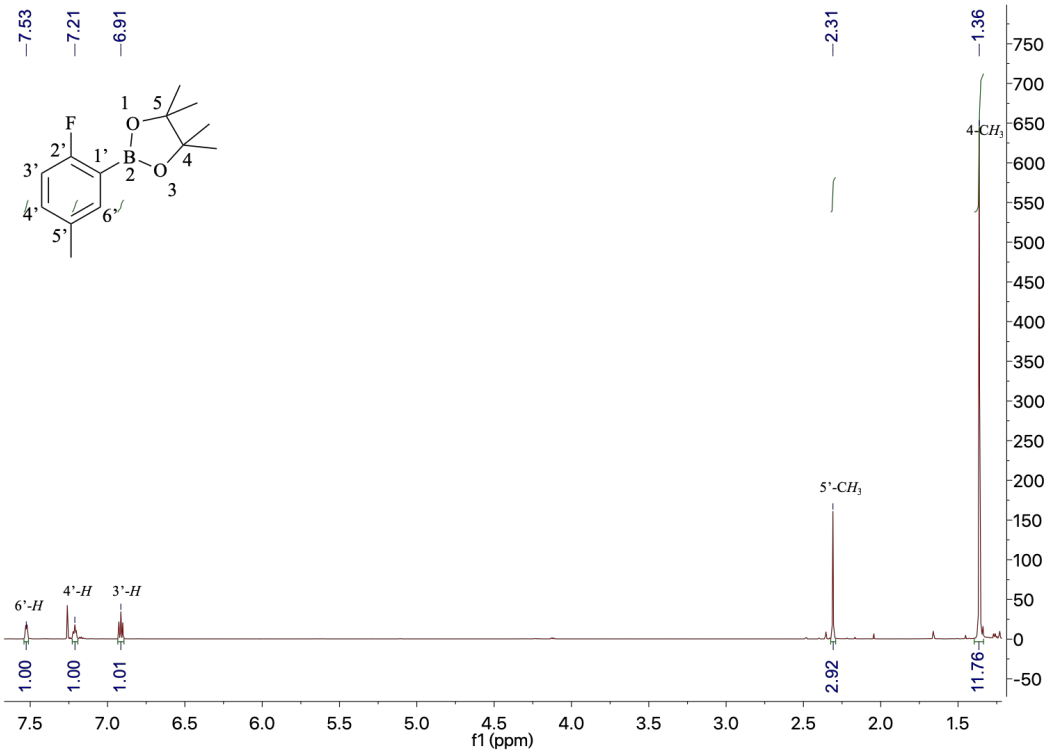


Figure 7 ^{1}H NMR spectrum (700 MHz, $CDCl_3$) of **61a**.

Assignments of ^{1}H and ^{13}C spectra using a combination of HSQC, HMBC, COSY and NOESY spectroscopic techniques unambiguously confirmed the identity of **61a**. In ^{1}H NMR analysis (Figure 7), the highly deshielded signal at 7.53 ppm was associated with 6'-*H*, which had an approximate 0.3 ppm downfield shift compared to 4'-*H* at 7.21 ppm arising from the introduction of the withdrawing Bpin group at C-1'. The triplet at 6.91 ppm with a larger coupling constant was assigned to the proton adjacent to the C-F bond (3'-*H*). The remaining resonances at 2.31 and 1.36 ppm, respectively, indicated three protons at the 5'-CH_3 and 4-CH_3 positions. In its ^{13}C NMR spectrum, the strong-coupling characteristic of a fluorine atom was shown more obviously, with $J_{C2'\text{-}F}$ of 250 Hz and $J_{C3'\text{-}F}$ of 25 Hz. The signal of the carbon attached to boron (C-1') was not found. This could be attributed to its broadened line caused by the quadrupolar boron nucleus.

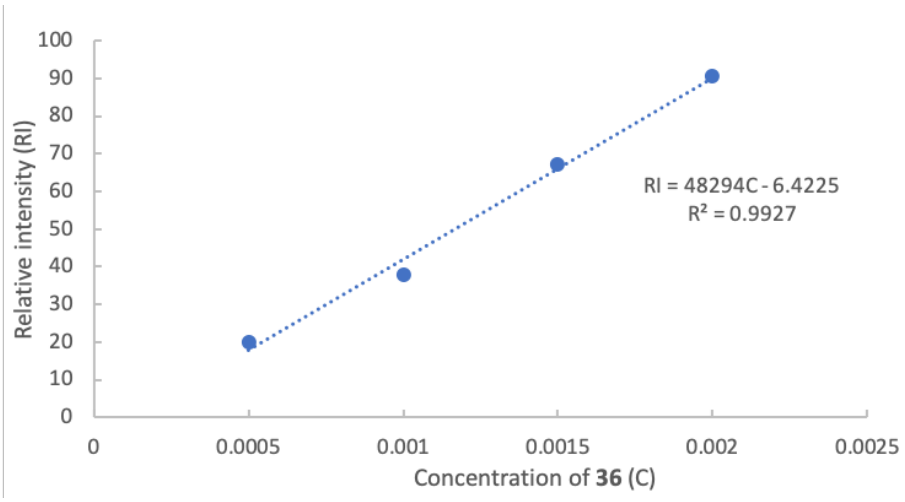


Figure 8 The calibration curve established for substrate **63**.

For the borylation of non-fluorine-containing substrates, conversion of the substrate was calculated using a calibration curve (e.g. Figure 8) plotted by a range of

concentration and integrated areas of the substrate peaks in the GC-MS. The ratio of products was calculated based on GC-MS analysis (e.g. Figure 9).

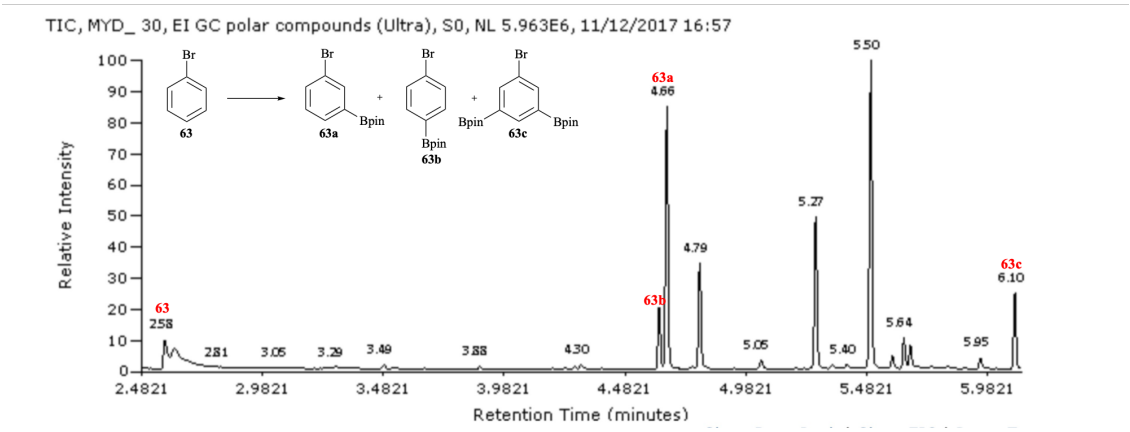


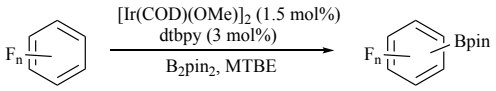
Figure 9 GC-MS analysis of borylation of **63**.

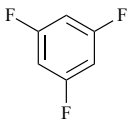
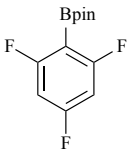
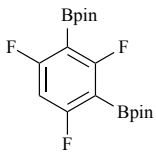
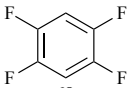
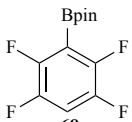
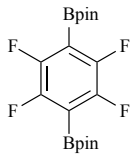
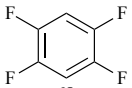
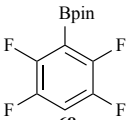
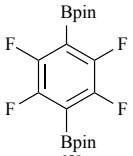
Having established a method, the comparative reactions were undertaken with a set of arenes using small variations in boron stoichiometry and reaction temperature (Table 5). Isolation of the resulting fluorinated boronic esters was performed by flash chromatography to give pure boronic esters in low to good yields. The lower yields of **61a** and **62a** reflected the challenges in the separation of the mono- and bis-borylated products. Fluorinated substrates afforded borylated products exclusively *ortho* to a C-F bond, whilst for the corresponding non-fluorinated arenes, *ortho*-positions were sterically disfavoured. This suggests that it is possible to overcome the hindrance of a small fluorine atom when compared with other functionalities in sterically controlled C-H borylation, which is consistent with established observations. Moreover, reaction of **66** (entry 11) showed that even two *ortho*-fluorine substituents could be tolerated.

Significantly, reactions of fluorinated substrates (e.g. entry 1) occurred faster than reactions of non-fluorinated analogues (e.g. entry 3), indicating the activating effect of the fluorine substituent. This observation was reinforced by the rapid activation of 3,5-difluorotoluene **66** (entry 11) and is consistent with the notion that C-H acidity correlates with reactivity.

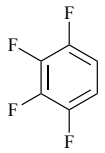
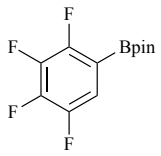
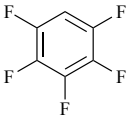
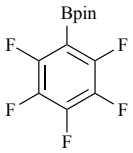
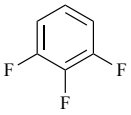
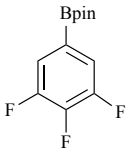
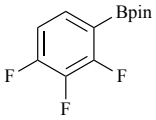
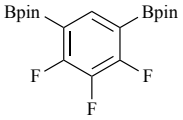
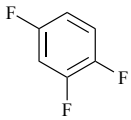
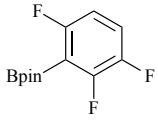
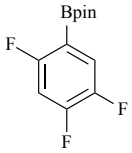
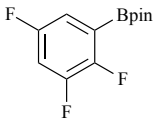
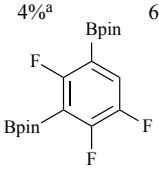
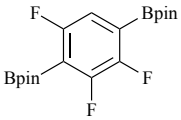
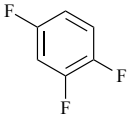
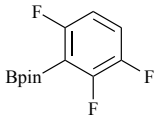
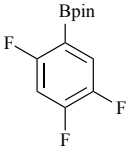
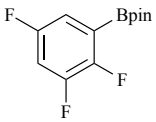
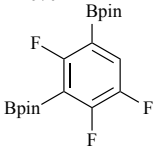
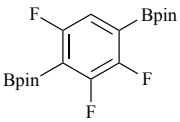
2.2 Borylation of polyfluorinated arenes

Given the observation that a fluorine substituent is tolerated in *ortho*-borylation and preliminary demonstration of the practicability of the $[Ir(COD)(OMe)]_2$-dtbpy-catalysed process, it was of interest to explore the effect of polyfluorinated arenes on effectiveness and regioselectivity of this reaction. Consequently, a simple systematic survey was performed as shown in Table 6.



Entry	Substrate	B_2pin_2/equiv.	Time/h	Temp./°C	Products	
1	 **67**	0.6	2	r.t.	 **67a** 64%[a] (49%[b,c])	 **67b** 17%[a] (1%[b,c])
2	 **68**	0.6	1	r.t.	 **68a** 43%[a] (27%[b,c])	 **68b** 41%[a] (19%[b,c])
3	 **68**	1.2	3	60	 **68a** 7%[a]	 **68b** 93%[a] (83%[b])

(a) Conversion was based on arene substrate and detected by ^{19}F NMR spectroscopy; (b) Yields for purified isolated products;
(c) Isolated as a mixture of two products.

4	 **69**	1.2	0.5	r.t.	 **69a** 96%[a] (42%[b])
5	 **70**	1.2	2	r.t.	 **70a** 95%[a] (62%[b])
6	 **71**	0.6	14	r.t.	 **71a** 22%[a]  **71b** 42%[a]  **71c** 22%[a]
7	 **72**	1.2	7	r.t.	 **72a** 4%[a]  **72b** 6%[a]  **72c** 6%[a]  **72d** 9%[a]  **72e** 74%[a]
8	 **72**	0.6	4	r.t.	 **72a** 20%[a]  **72b** 8%[a]  **72c** 19%[a]  **72d** 2%[a]  **72e** 27%[a]

(a) Conversion was based on arene substrate and detected by ^{19}F NMR spectroscopy; (b) Yields for purified isolated products;
(c) Isolated as a mixture of two products.

Table 6 Borylation of polyfluorinated arenes.

All of the substrates were borylated using the procedure described in the previous section. Product identity was again primarily determined using a combination of GC-

MS and ^{19}F NMR analysis of the crude mixture, and NMR assignments of the purified isolated products. For each reaction, the conversion of the fluoroarene and the ratio between different isomers were calculated based on integrations of peaks in ^{19}F NMR spectra.

Borylation of **67** will be discussed as an example. Once completed, GC-MS analysis of the crude reaction showed peaks of molecular ions at 258 and 384 m/z, indicating the formation of **67a** and **67b**. ^{19}F NMR analysis indicated an approximate 4 : 1 ratio of **67a** to **67b**, with both signals of mono-borylated product **67a** (-97.2 and -103.9 ppm) shifted downfield with respect to the signals of the bis-borylated product **67b** (-86.4 and -93.8 ppm). This was due to the installation of an additional boronate group. The remaining trace at -107.4 ppm indicated an 81% conversion of substrate **67** after 2 hours. The crude reaction mixture was subjected to flash column chromatography resulting in a mixture of **67a** and **67b** (49 : 1 by ^{19}F NMR) in 50% isolated yield which was then analysed using ^{1}H, ^{13}C, and ^{11}B NMR techniques.

Although **67b** was clearly detected by GC-MS and ^{19}F NMR analysis, further analysis of the reaction mixture proved that some of the peaks were undetectable in ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectrum of the isolated mixture, the peak for the aryl proton at 6.64 ppm was split into a multiplet due to coupling with three fluorine atoms. The remaining peaks (1.37 and 1.35 ppm), which were respectively assigned to methyl groups in **67a** and **67b**, roughly presented a ratio of 24.5 : 1 and correlated with the

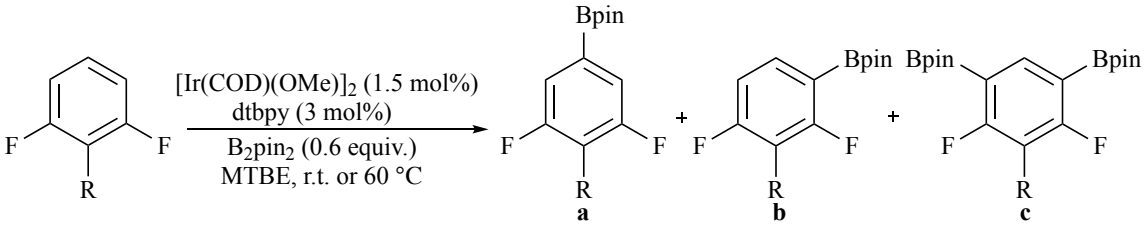
product ratio (**67a**/**67b** = 49 : 1) calculated from ^{19}F NMR spectroscopy. ^{13}C NMR analysis again did not show the signals for carbons attached to Bpin group.

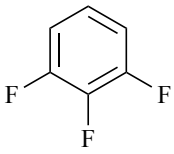
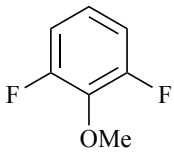
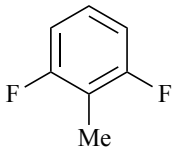
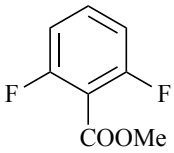
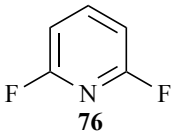
In summary, the polyfluorinated arenes in Table 6 all readily undergo borylation reactions at room temperature to afford high conversion and moderate to high isolated yields of the resulting products. And all of these substrates proved to be more reactive than the mono-fluoroarenes discussed in the previous section. This observation is consistent with the established report by Ishiyama, Miyaura, Hartwig *et al.*, who stated that electron-deficient arene substrates are more active than the electron-rich substrates.[10] Separation of the polyfluorinated boronic esters proved to be difficult. For these products (Table 6, entry 6) a sequential Suzuki-Miyaura cross-coupling process (Section 2.5) was carried out in the hope of facilitating separation by increasing the difference in the polarity of the products.

With the small van der Waals radius of a fluorine atom, *ortho*-borylation reactions were easily processed and two *ortho* fluorines were again proved to be tolerated. Interestingly, reaction of 1,2,3-trifluorobenzene **71** (entry 6) provided a 1 : 3 ratio of 5- to 4-borylated products, suggesting that the *ortho*-activating effect of fluorine substituents played an important role in this process. Results of the borylation of **72** were complicated by the formation of multi-borylated products, such that the relative reactivity of di-*ortho*-fluorine C-H bond remains unknown (entries 7 and 8). Although this multi-borylation could be controlled by reducing the stoichiometry of the boron sources that was added,

it was not possible to identify conditions for exclusive mono-borylation.

2.3 Borylation of 1,3-difluoroarenes



Entry	Substrate	Temp./°C	Time/h	Conv./%[a]	Ratio (**a** : **b** : **c**)[b]	Yield/%[c]
1	 **71**	r.t.	14	86	1: 2 : 1	—
2	 **73**	r.t.	16	74	1 : 1.2 : 0.2	—
3		60	4	87	1 : 1.1 : 0.2	67
4	 **74**	r.t.	14	86	2 : 1 : 0.2	65
5		60	2	91	2 : 1 : 0.3	61
6	 **75**	r.t.	19	92	3 : 1 : 0.3	75
7	 **76**	r.t.	3	89	4 : 1 : 0.2	77

(a) Conversion was based on arene substrate and detected by ^{19}F NMR spectroscopy; (b) Ratio was calculated by ^{19}F NMR spectroscopy; (c) Overall isolated yields (see experimental section for details).

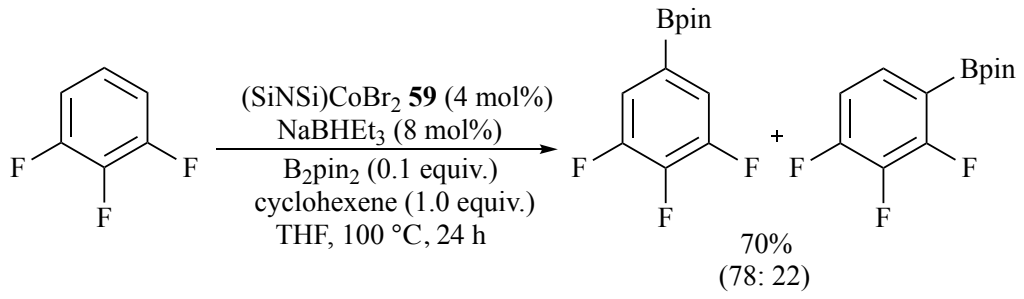
Table 7 Borylation of 1,3-difluoroarenes.

As discussed in the last section, the considerable amount of 4-borylated product

afforded by 1,2,3-trifluorobenzene **71** indicated a strong activating effect of an *ortho*-fluorine substituent. In order to further explore the balance between steric and electronic effects afforded by a fluorine atom, a group of 1,3-difluoroarene substrates with various 2-substitutents was then examined (Table 7). Borylation of these 1,3-difluoroarenes and identification of the resulting boronated products were performed in a similar fashion to that used for polyfluorinated arenes in Table 6.

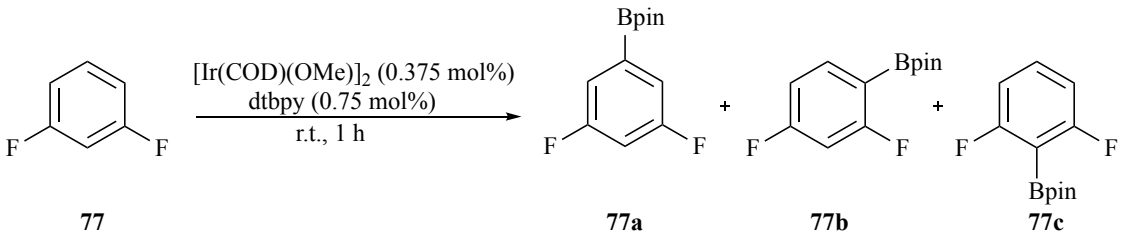
Reflecting its unhindered nature, the 1,3-difluoro-2-substituted arene scaffold proved to be a viable substrate affording good to excellent conversions for the resulting boronic esters at room temperature. Good overall isolated yields were achieved, although it should be noted that separation of each isomer remained a challenge. Each reaction in Table 7 gave a similar mixture of 4-, 5-, and minor di-borylated products, with regioselectivity independent of the reaction temperature (entries 2 and 3, entries 4 and 5). An overall increasing proportion of 5-borylated isomers was observed that correlated with the order of electron-withdrawing ability of the 2-substitutent (pyridine>CO_2Me>Me>OMe, entries 2 to 7), indicating the presence of an inherent electronic effect in the borylation reactions. However, one noticeable exception was that 1,2,3-trifluorobenzene **71** (entry 1), which has a relatively electron-withdrawing 2-substituent, favoured the formation of 4-isomers. This resulted contrasts with the only other reported borylation of this substrate (Scheme 30)[69] and an explanation for this observation is not immediately obvious. Finally, in contrast to the reaction of the parent pyridine which exhibits a preference for the 3-borylated product, **76** (entry 7) reacted

rapidly with high selectivity for borylation at the 4-position. This unexpected observation will be further studied through borylation of a range of fluorinated pyridine substrates (Section 2.4).



Scheme 30 Borylation of **71** reported by Cui *et al.*[69]

To further investigate the *ortho*-directing effect afforded by fluorine substituents, attention was turned to the borylation of 1,3-difluorobenzene **77**. With the presence of four unhindered positions in this substrate, an initial experiment with **77** was undertaken using a low stoichiometry of boron source to reduce the complications of polyborylation as previously reported by Smith *et al.*[19] Although Smith's work was carried out with HBpin and THF, in the expectation that this modification should not affect the regioselectivity, in this study it was decided to use diboron reagent B_2pin_2 and MTBE (Scheme 31). Charging a Schlenk tube with a combination of $[Ir(COD)(OMe)]_2$ (0.375 mol%), dtbpy (0.75 mol%), and B_2pin_2 (0.125 equiv.), followed by flushing the mixture with nitrogen and the addition of anhydrous MTBE, gave the black active catalyst species. Substrate **77** was then added. The reaction mixture was stirred at room temperature for 1 hour before being monitored using ^{19}F NMR spectroscopy.

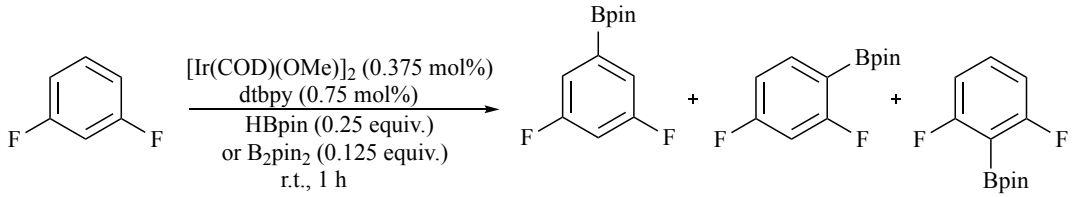


	Boron source	Solvent	Ratio (a : b : c)
Smith's work[19]	HBpin (0.25 equiv.)	THF	50 : 33 : 17[a]
This work	B_2pin_2 (0.125 equiv.)	MTBE	29 : 24 : 47[b]

(a) calculated by GC-MS, (b) calculated by ^{19}F NMR

Scheme 31 Borylation of **77** using HBpin and B_2pin_2.

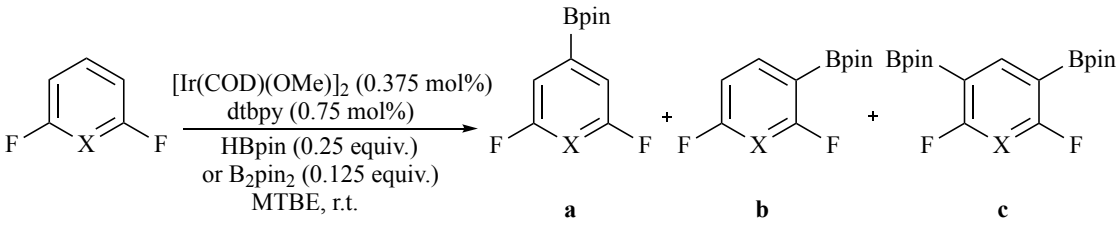
Surprisingly, in contrast to the ratio reported in the literature for the reaction using HBpin which led to preferential activation of the least hindered 5-position (**77a**),[19] borylation of **77** carried out with B_2pin_2 appeared to favour the di-*ortho*-fluorine 2-position (**77c**). This difference was also observed in reactions of **77** in which THF, MTBE, 1,4-dioxane, and mesitylene were used as solvents (Table 8, entries 1-9). In contrast, reactions performed in hexane gave identical results for both boron sources (Table 8, entries 10 and 11). Moreover, there was no difference in the ratios of products provided by HBpin and B_2pin_2 in the reactions with other 1,3-difluoroarene analogues (Table 9).



Entry	Boron source	Solvent	Ratio (**a** : **b** : **c**)[a]
1 (Ref. 19)	HBpin	THF	50 : 33 : 17
2 (Repeat ref. 19)	HBpin	THF	46 : 28 : 26
3	B_2pin_2	THF	32 : 25 : 43
4	HBpin	MTBE	39 : 26 : 35
5	B_2pin_2	MTBE	29 : 24 : 47
6	HBpin	1,4-Dioxane	43 : 30 : 27
7	B_2pin_2	1,4-Dioxane	25 : 21 : 54
8	HBpin	Mesitylene	39 : 25 : 36
9	B_2pin_2	Mesitylene	22 : 18 : 60
10	HBpin	Hexane	29 : 23 : 48
11	B_2pin_2	Hexane	25 : 24 : 51

(a) Ratio was calculated by ^{19}F NMR spectroscopy.

Table 8 Borylation of **77** with HBpin and B_2pin_2 in different solvents.

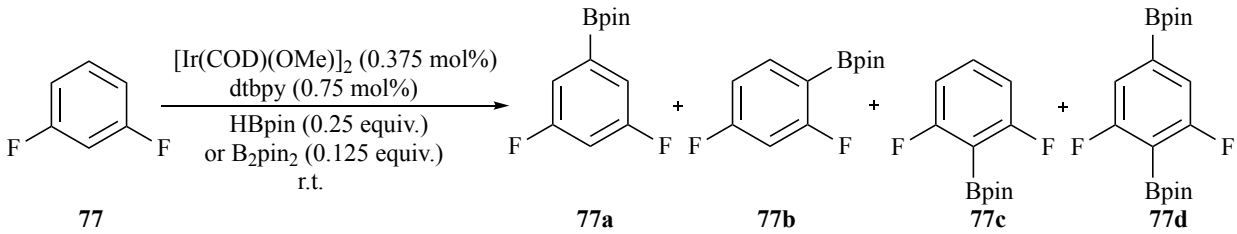


Entry	X	Boron source	Time/h	Conv. of boron/%[a]	Rario (**a** : **b** : **c**)[b]
1	C-F **71**	B_2pin_2	1	76	29 : 71 : 0
2	C-F **71**	HBpin	1	19	31 : 69 : 0
3	C-F **71**	B_2pin_2	23	100	28 : 68 : 4
4	C-F **71**	HBpin	36	100	31 : 66 : 3
5	C-OMe **73**	B_2pin_2	1	48	40 : 58 : 2
6	C-OMe **73**	HBpin	1	20	40 : 60 : 0
7	C-Me **74**	B_2pin_2	1	26	63 : 37 : 0
8	C-Me **74**	HBpin	1	13	68 : 32 : 0
7	C-Me **74**	B_2pin_2	4	100	66 : 34 : 0
8	C-Me **74**	HBpin	51	100	70 : 30 : 0
11	C-CO_2Me **75**	B_2pin_2	1	100	72 : 27 : 1
12	C-CO_2Me **75**	HBpin	1	100	77 : 23 : 0
13	N **76**	B_2pin_2	1	88	79 : 21 : 0
14	N **76**	HBpin	1	19	81 : 19 : 0

(a) Conversion of boron was calculated based on the amounts of products in ^{19}F NMR spectra using hexafluorobenzene as an internal standard. (b) Ratio was determined by ^{19}F NMR spectroscopy.

Table 9 Borylation of 1,3-difluoro-2-substituent arenes using HBpin and B_2pin_2

The observations discussed above indicated an unusual reactivity of the 2-position in **77** in the reaction with B_2pin_2. To confirm this reactivity, a more detailed survey which monitored the borylation of **77** over time, was carried out (Table 10). The reaction in each entry was performed three times to obtain an average conversion and ratio. For each experiment, conversion of boron was determined from the amount of the products formed, which was calculated based on ^{19}F NMR spectroscopic analysis using hexafluorobenzene as an internal standard.



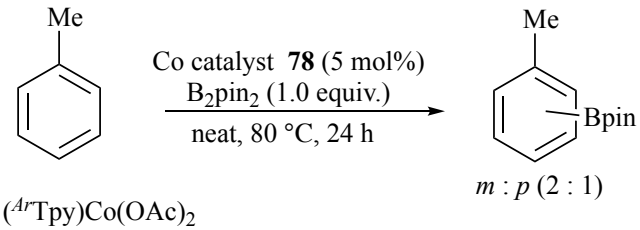
Entry	Solvent	Time/h	Boron source	Conv. of boron/%[a]	Ratio (**a** : **b** : **c** : **d**)[b]
1	THF	1	B_2pin_2	58	35 : 23 : 38 : 4
2	THF	1	HBpin	24	49 : 27 : 23 : 1
3	THF	10	B_2pin_2	82	40 : 25 : 29 : 6
4	THF	10	HBpin	56	50 : 27 : 19 : 4
5	THF	24	B_2pin_2	60	39 : 25 : 31 : 5
6	THF	24	HBpin	21	50 : 29 : 19 : 2
7	MTBE	1	B_2pin_2	69	31 : 23 : 41 : 5
8	MTBE	1	HBpin	20	41 : 27 : 31 : 1
9	MTBE	10	B_2pin_2	62	35 : 25 : 34 : 6
10	MTBE	10	HBpin	47	44 : 27 : 26 : 3
11	MTBE	24	B_2pin_2	63	35 : 24 : 36 : 5
12	MTBE	24	HBpin	42	46 : 27 : 24 : 3

(a) Conversion of boron was calculated based on the amounts of products in ^{19}F NMR spectra using hexafluorobenzene as an internal standard. (b) Ratio was determined by ^{19}F NMR spectroscopy.

Table 10 Selectivities in the borylation of **77** after 1, 10 and 24 hours.

Ratios provided by HBpin were consistent over time in both THF and MTBE, although the lower conversion after 24 hours (e.g. Table 10, entry 6) compared with that after 10

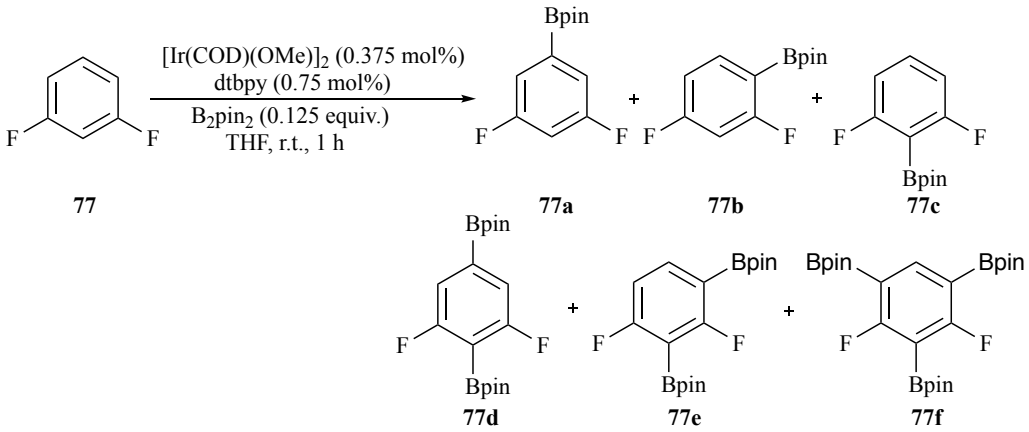
hours (e.g. Table 10, entry 4) indicated that the partial decomposition of borylated products was occurring. In comparison, ratios given by B_2pin_2 were variable over time in both solvents. However, these ratios do not reflect the exact selectivities afforded by B_2pin_2 because HBpin, the byproduct in the first borylation, would continue to react in the second cycle (see mechanism in Scheme 6, page 12). In other words, both B_2pin_2 and HBpin reacted with **77** in this system. Reflecting this, it was of interest to sequester HBpin in the reaction system. The inhibitory effect of LiOMe on HBpin through the formation of a methoxide-borane adduct was suggested by Chirik *et al.* in the Co-catalysed C-H borylation of toluene (Scheme 32).[75] Based on this report, 0.125 equivalent of lithium methoxide was added to the standard reaction conditions (Scheme 33). Disappointingly, this attempt to sequester HBpin was unsuccessful, with no significant effect on ratios being observed.



78: (^{Ar}Tpy)Co(OAc)$_2$
(^{Ar}Tpy = 4′-(4-N,N′-dimethylaminophenyl)-2,2′:6′,2″-terpyridine)

Additive	Yield/%
—	56
HBpin (10 mol%)	29
LiOMe (10 mol%)	80

Scheme 32 Inhibitive activity of LiOMe in HBpin in borylation reaction.[75]



Entry	Additive	Temp./°C	Conv. of boron/%[a]	Rario (**a** : **b** : **c** : **d** : **e** : **f**)[b]
1	LiOMe (0.125 equiv.)	80	89	45 : 33 : 17 : 3 : 1 : 1
2	—	80	100	41 : 32 : 22 : 4 : 0 : 1
3	LiOMe (0.125 equiv.)	r.t.	45	32 : 23 : 42 : 3 : 0 : 0
4	—	r.t.	52	34 : 23 : 39 : 4 : 0 : 0

(a) Conversion of boron was calculated based on the amounts of products in ^{19}F NMR spectra using hexafluorobenzene as an internal standard. (b) Ratio was determined by ^{19}F NMR spectroscopy.

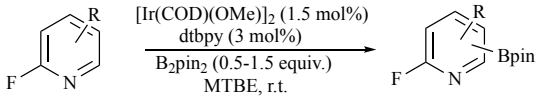
Scheme 33 An attempt to sequester HBpin with the presence of LiOMe

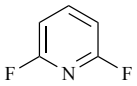
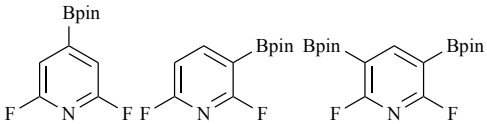
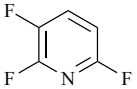
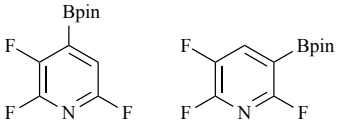
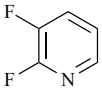
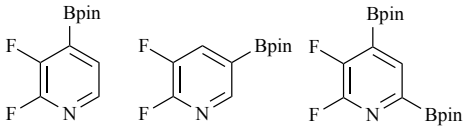
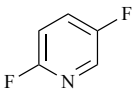
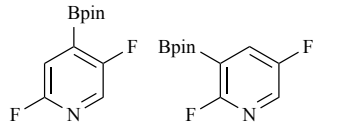
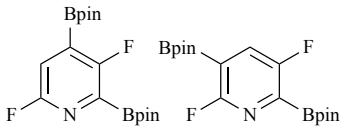
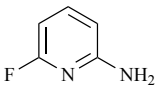
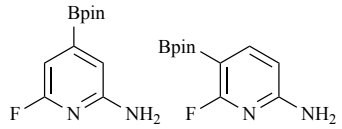
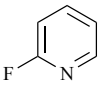
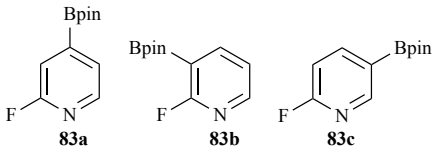
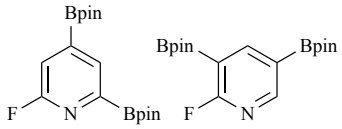
Whilst the cause of the difference in the behaviour of HBpin and B_2pin_2 remains uncertain, the different product outcomes suggested a difference in the key regioselectivity inducing step. This is in contrast to the generally accepted mechanism (Scheme 6, page 12) in which both cycles use a common process for this step. Time prevented a more detailed investigation onto this issue, but this remains a significant future objective.

2.4 Borylation of fluorinated pyridines

Having successfully borylated polyfluoroarenes with high conversion, attention was turned to fluorinated pyridine substrates. As discussed in the previous section, the reaction of 2,6-difluoropyridine **76** favoured the formation of 4-borylated product,

whereas the unsubstituted pyridine gave a preference for the 3-isomer. Consequently, the behaviour of a series of 2-fluoropyridine substrates in Ir-catalysed C-H borylation reactions was examined (Table 11).



Entry	Substrate	Products	Conditions	Conv./%[a]	Yield/%[b]
1	 **76**	 **76a** **76b** **76c**	A	89 (4 : 1 : 0.2)	77
2	 **79**	 **79a** **79b**	B	89 (6 : 1)	—
3	 **80**	 **80a** **80b** **80c**	B	91 (6 : 1 : 0.5)	—
4	 **81**	 **81a** **81b**  **81c** **81d**	C	90 (1.6 : 1 : 0.1 : 0.1)	—
5	 **82**	 **82a** **82b**	D	82 (2 : 1)	50
6[c]	 **83**	 **83a** **83b** **83c**  **83d** **83e**	E	89 (57 : 17 : 19 : 2 : 5)	—

Condition A: B_2pin_2 (0.6 equiv.), 3 h; Condition B: B_2pin_2 (0.6 equiv.), 11 h; Condition C: B_2pin_2 (0.6 equiv.), 17 h;
Condition D: B_2pin_2 (1.5 equiv.), 23 h; Condition E: B_2pin_2 (0.5 equiv.), 24 h;
(a) Conversion was determined by ^{19}F NMR spectroscopy; (b) Overall isolated yields (see experimental for details); (c) see Ref. 26.

Table 11 Borylation of fluorinated pyridines.

Borylation of **79-82** was run using the previously described method. Upon completion, the reaction mixture was either subjected to flash column chromatography to isolate the resulting boronic esters (Table 11, entries 1 and 5) or applied into a sequential Suzuki-Miyaura reaction with 2-iodopyridine to synthesise the corresponding cross-coupled arenes (Table 11, entries 2-4). Product identity was based on a combination of ^{1}H NMR, GC-MS analysis of the crude reaction mixture and full assignments of the purified isolated products. Conversion of each substrate and the ratios of different isomers were determined by ^{1}H NMR spectroscopy. Borylation of 2-fluoropyridine **83** has been carried out in previous work within the group.[26]

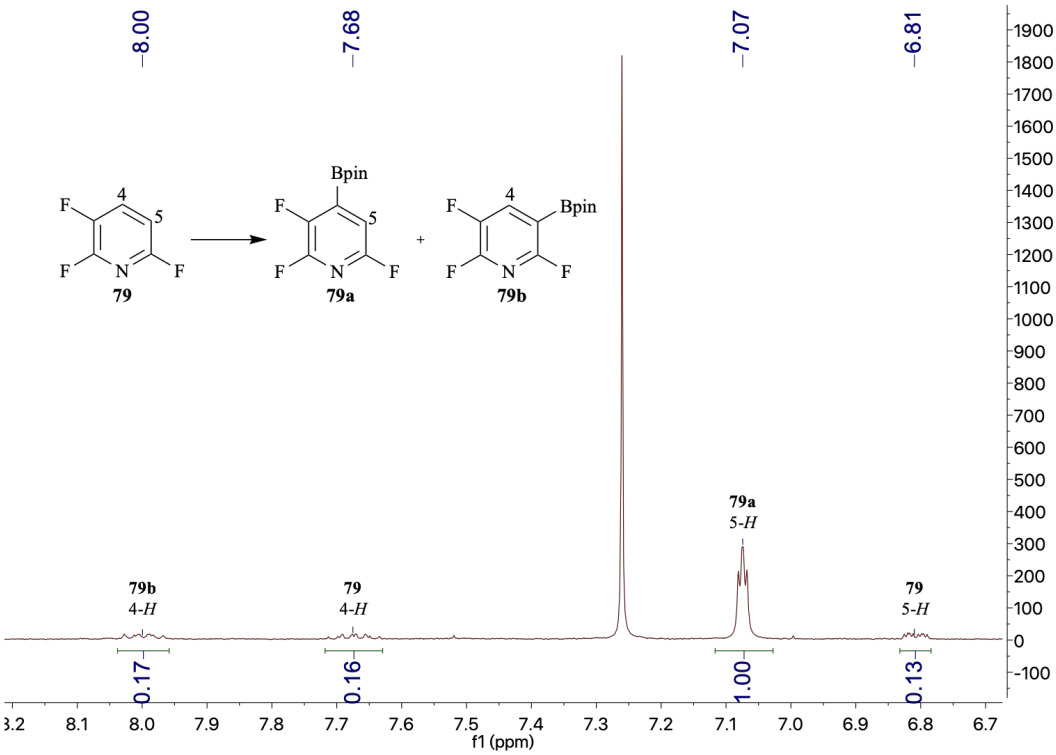


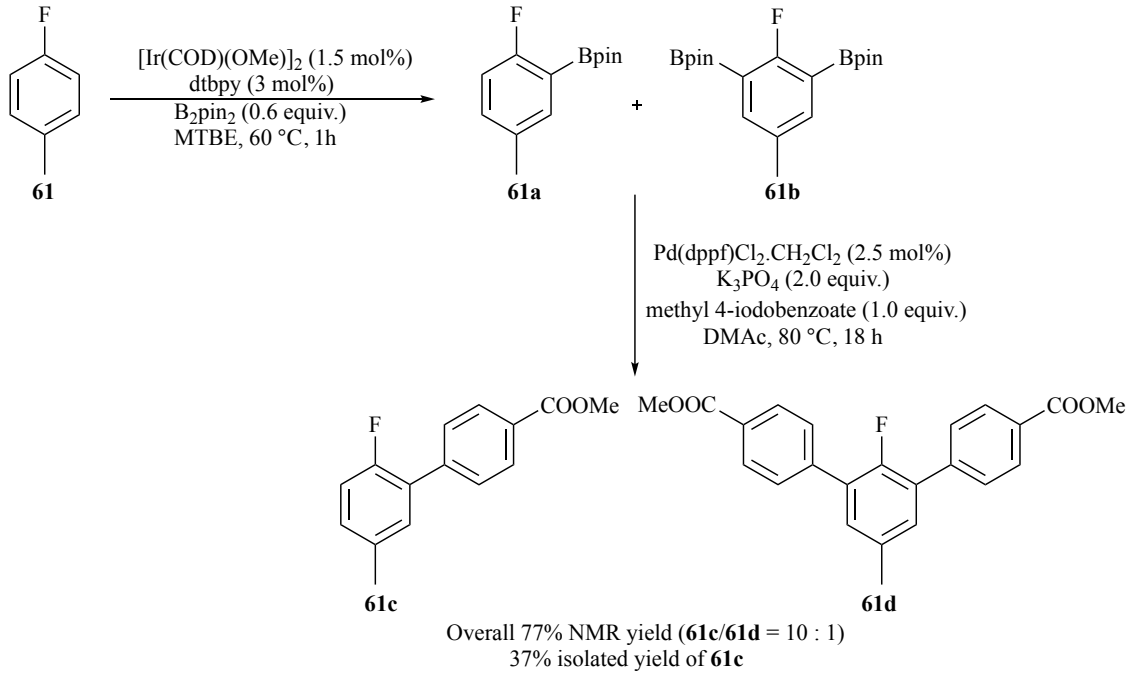
Figure 10 ^{1}H NMR spectrum of the crude mixture of borylation of **79**.

For example, for the borylation of **79**, analysis of the crude mixture by GC-MS showed two M^+ peaks at m/z = 133, demonstrating the formation of two mono-borylated isomers. In the aromatic area of ^{1}H NMR spectrum (Figure 10), two signals presenting in 7.07 and 8.00 ppm indicated an approximate 6 : 1 ratio of **79a** to **79b**. Integration of the remaining two peaks at 6.81 and 7.68ppm, which could be assigned to the two protons of the pyridine ring in the substrate, showed an 89% conversion of **79**. The higher chemical shift of the pyridyl proton in the product (e.g. 7.07 ppm) compared to that in the substrate (e.g. 6.81 ppm) was consistent with the installation of an electron-withdrawing boronate moiety adjacent to this position. Due to the difficulty in separating **79a** and **79b**, the reaction mixture was then subjected to a sequential Suzuki-Miyaura cross-coupling reaction. Details for this process will be discussed in Section 2.5.

Analogous to the previous set borylations of the fluoroarenes (Tables 5, 6, and 7), fluorinated pyridine substrates in Table 11 afforded high conversions and moderate to good isolated yields at room temperature. For all substrates, reactions occurred preferentially at the 4-position as opposed to the 3-position, regardless of which position was more sterically accessible. Trace amounts of 2-borylated products could be observed in both ^{1}H and ^{19}F NMR spectra of the crude reaction (entries 3, 4, and 6). However, as noted in the review, these α-pyridyl boronic esters are very unstable and undergo facile protodeboronation. Subsequently, these products decomposed on the acidic silica column or during the Suzuki-Miyaura cross-coupling processes.

2.5 Iridium-catalysed C-H borylation/Suzuki-Miyaura cross-coupling strategies

Throughout this work, separation and isolation of fluorinated boronic esters had proved challenging. To aid isomer identification, these mixtures were transformed into biaryl molecules through a Suzuki-Miyaura cross-coupling reaction. This transformation is of potential interest as these fluorinated boronic esters have been described as difficult substrates[70] and a general solution would be of use in synthesis.



Scheme 34 One-pot C-H borylation/Suzuki-Miyaura cross-coupling sequences.

An initial attempt was to perform a one-pot C-H borylation/Suzuki-Miyaura cross-coupling sequences on a simple fluoroarene **61** (Scheme 34) using the cross-coupling conditions developed in the group by Wright (unpublished work). Borylation of 1-fluoro-4-methylbenzene **61** as before using $[Ir(COD)(OMe)]_2$ (1.5 mol%), dtbpy (3.0

mol%), and B_2pin_2 (0.6 equiv.) at 60 ℃ for 1 hour gave a mixture of mono- and bis-borylated products. After quenching in air, the mixture was cooled and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (2.5 mol%), K_3PO_4, and methyl 4-iodobenzoate in DMAc were then added. The reaction was allowed to proceed at 80 ℃ under nitrogen for 18 hours. A 77% NMR yield of the cross-coupled products was obtained as a mixture of **61c** and **61d**, as indicated by GC-MS analysis of the crude mixture which showed two M^+ peaks with 244 and 378 m/z. The product identity of **61c** and **61d** was assigned based on the degree of the upfield shift of the fluorine signal (around 15 ppm) of **61a** and **61b** which resulted from replacement of a Bpin group with an aryl group. Following an aqueous workup, flash column chromatography afforded a 37% isolated yield of **61c**, which was characterised by ^1H, ^{13}C, and ^{19}F NMR techniques. Full assignments of ^1H and ^{13}C spectra confirmed the identity of **61c**. In its ^1H spectrum (Figure 11), the two doublets at 8.10 and 7.62 ppm, which had similar integrations and *J*-couplings were respectively assigned to 3-*H* and 2-*H*. The broad signal presenting at 7.05 ppm (J = 10.5 Hz) was in agreement with the proton *ortho* to a C-F bond. Correlation in the HMBC spectrum between C-1 and the signal at 7.24 ppm confirmed this proton as 6'-*H*. Therefore, the remaining peak in the aromatic area (7.14 ppm), which exhibited a weak complementary W-coupling with 6'-*H*, was assigned to the proton at the 4' position. Additionally, resonances at 3.94 and 2.37 ppm, respectively, indicated the three protons of the methoxy and methyl groups.

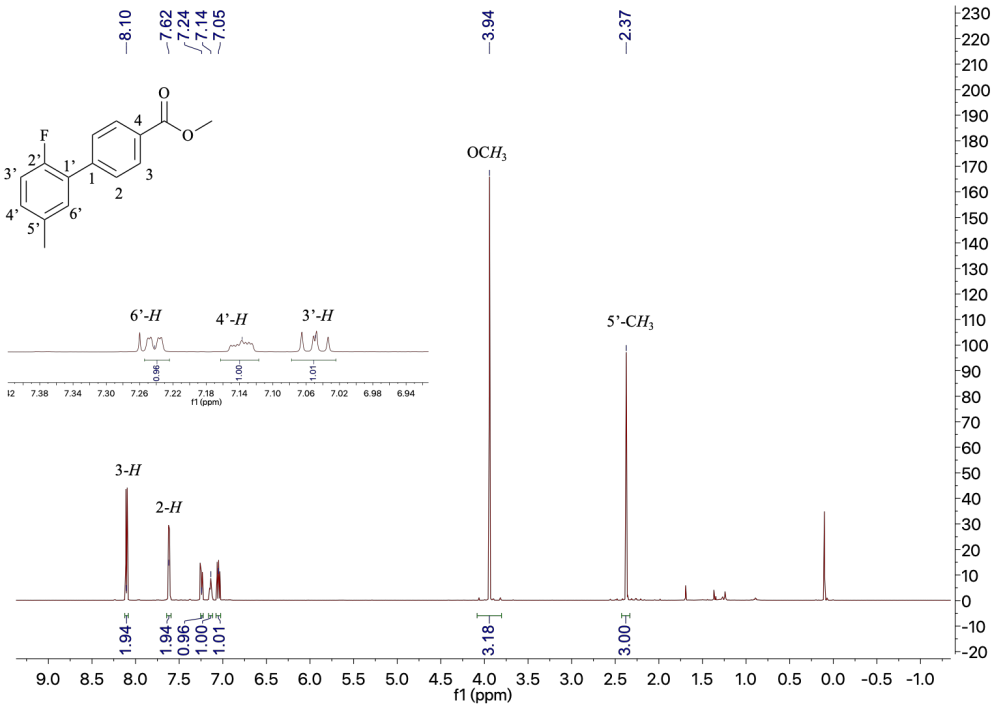
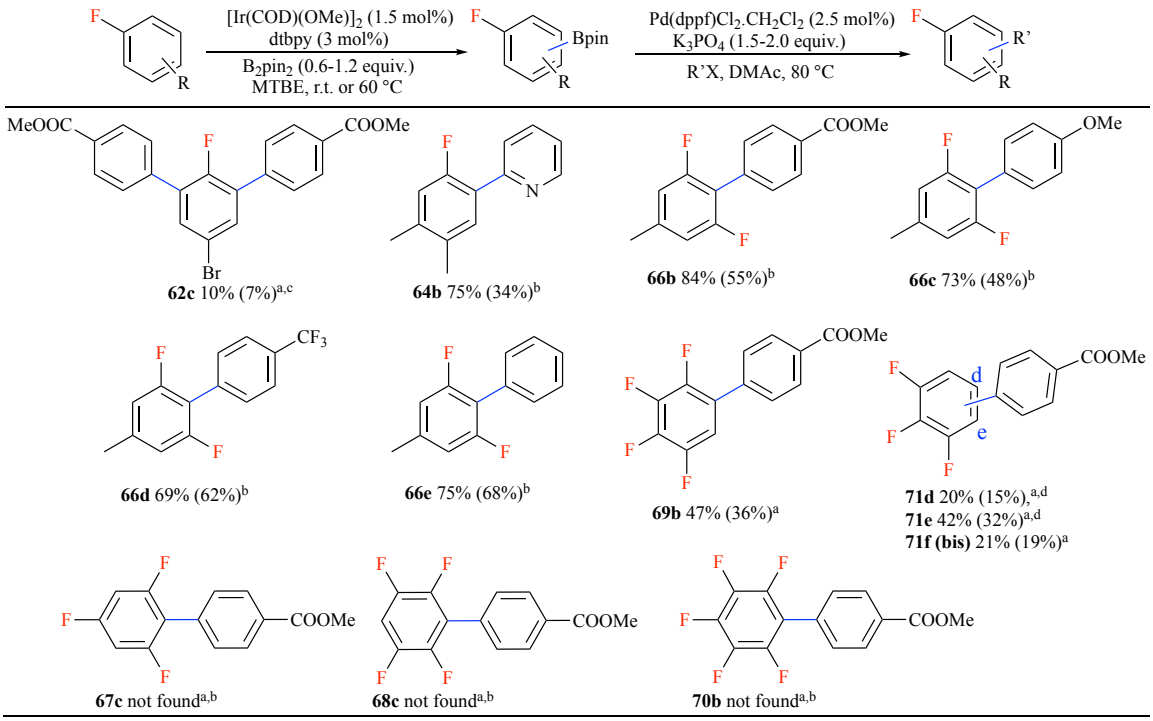


Figure 11 1H NMR spectrum of **61c**.

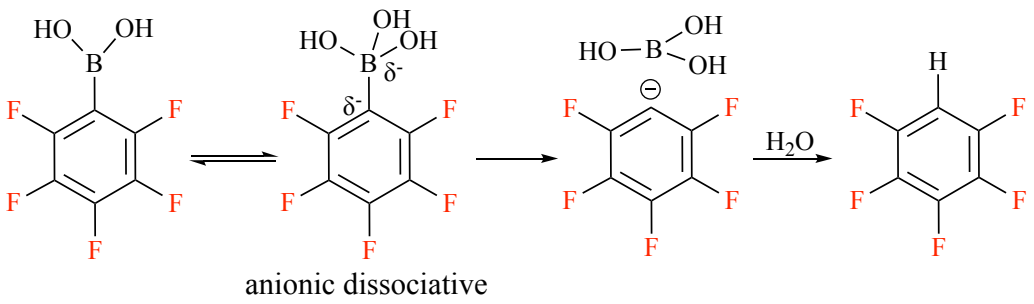


Reported values are NMR yields and values in parentheses are isolated yields.
(a) Synthesized from one-pot borylation/cross-coupling reactions and yields are based on fluoroarenes;
(b) Synthesized from isolated boronic esters and yields are based on fluorinated arylboronic esters;
(c) 70% NMR yield of monocross-coupled product;
(d) Isolated as a mixture of two monocross-coupled products.

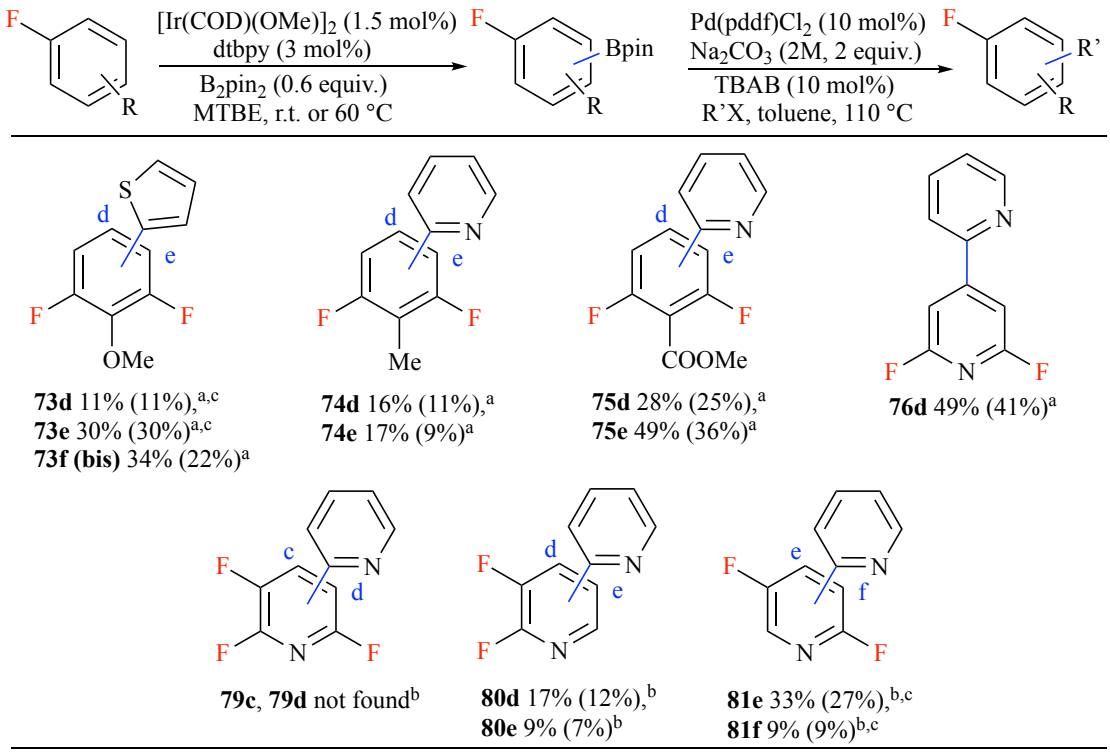
Table 12 Suzuki-Miyaura cross-coupling reactions catalysed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$.

With this efficient procedure established to be viable for fluorinated boronic esters, a group of substrates was chosen to demonstrate the versatility of the cross-coupling reactions with aryl halides bearing electron-deficient and electron-rich substituents (Table 12).

Transformations of simple fluoroarene substrates to fluorinated biaryls using this protocol were successfully performed to afford high overall NMR yields and moderate to good isolated yields. However, the more highly polyfluorinated substrates tended to result in lower NMR yields (e.g. **69b**). In particular, reactions of boronate substrates **67a**, **68a**, and **70a**, which have di-*ortho*-fluorine positions were not successful, with only the protodeborylated arenes being detected. This rapid protodeboronation was attributed to the easy generation of an *ipso*-aryl carbanion facilitated by the *o*-fluorine atoms (Scheme 35).[76]



Scheme 35 Mechanisms for base-catalysed fluorinated aryl boronic acid protodeboronation.[76]

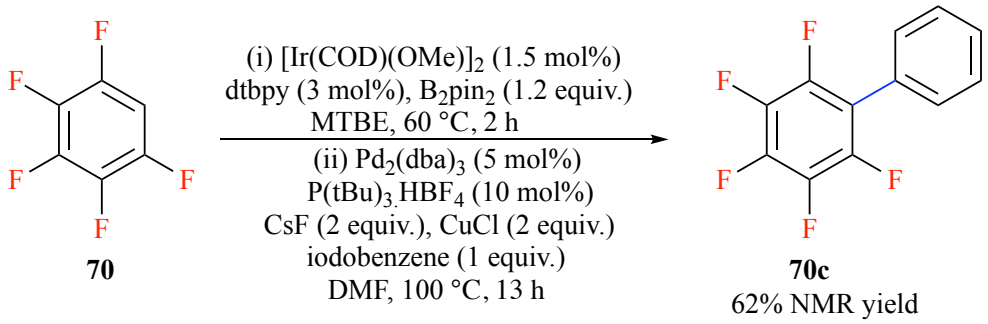


Reported values are NMR yields and values in parentheses are isolated yields.
(a) Synthesized from purified boronic esters and yields are based on fluorinated arylboronic esters;
(b) Synthesized from one-pot borylation/cross-coupling reactions and yields are based on fluoroarenes;
(c) Isolated as a mixture of two monocross-coupled products.

Scheme 36 Suzuki-Miyaura cross-coupling reactions catalysed by Pd(dppf)Cl_2.

With this in mind alternative procedures for cross-coupling reactions were considered. In a first approach adapted from a patent reported by Janssen Pharmaceutica N.V. (Scheme 36),[77] a mixture of boronic esters **73a**, **73b**, and **73c** was treated with Pd(dppf)Cl_2 (10 mol%) and tetra-*n*-butylammonium bromide (TBAB, 10 mol%). After being flushed with nitrogen, 2-iodothiophene and dry toluene were added. This mixture was then cooled to 0 °C and aq. Na_2CO_3 was added dropwise. Heating the reaction at 110 °C under nitrogen for 23 hours afforded overall 75% NMR yield of cross-coupled products. The subsequent aqueous workup and flash column chromatography afforded

overall 63% isolated yield of the resulting products (**73d**, **73e**, and **73f**), which were then characterised by ^{1}H, ^{13}C, and ^{19}F NMR techniques. This method was then extended to other borylated arenes. In most cases, the desired fluorinated biaryls could be obtained albeit sometimes as an isomer mixture. However, the yields were not great, indicating that the reactions of these fluorinated boronic esters remain problematic. In particular, the more highly fluorinated pyridylboronic esters resulted in lower NMR yields, with 100% protodeboronation observed for the attempted reaction of aryl boronic esters **79a** and **79b**.

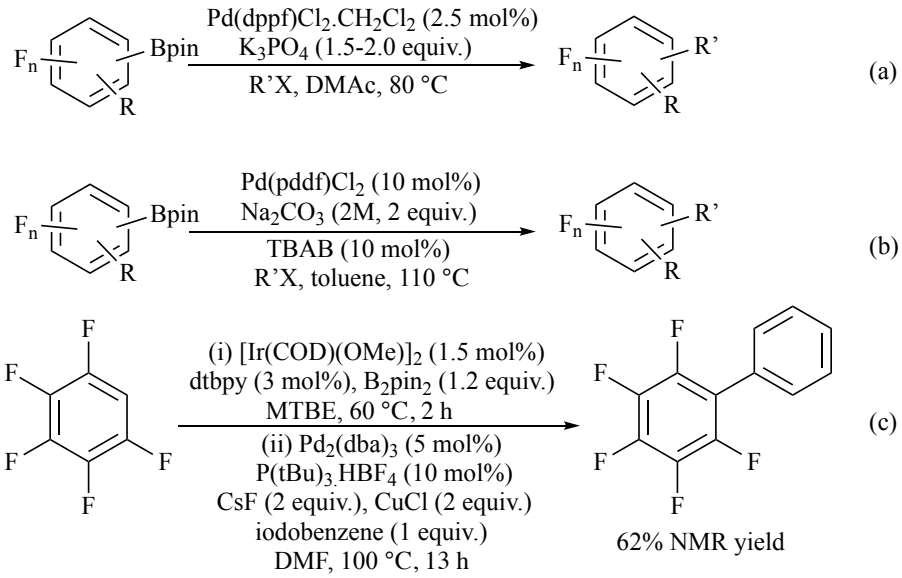


Scheme 37 An anhydrous protocol for Suzuki-Miyaura cross-coupling reaction.

To circumvent these problems, an anhydrous reaction condition that was developed within the group by Hones (unpublished work) was attempted using CsF as a source of F^- to activate the boronic esters (Scheme 37). Following the transformation of pentafluorobenzene **70**, to the crude boronate ester, the cross-coupling reaction was achieved by the addition of $Pd_2(dba)_3$ (5 mol%), CsF (2.0 equiv.), $P(tBu)_3{\cdot}HBF_4$ (10 mol%), CuCl, (2.0 equiv.), and iodobenzene in DMF. After heating at 100 °C under nitrogen for 13 hours, an overall 62% NMR yield of biphenyl **70c** could be obtained.

Following an aqueous workup, flash column chromatography afforded 37% isolated yield of **70c**, which was then characterised by ^{1}H, ^{13}C and ^{19}F NMR techniques. This attempt proved the effectiveness of this $Pd_2(dba)_3$-catalysed system for polyfluorinated boronic ester substrates. Regrettably, time prevented a full study of the scope and limitation of this system.

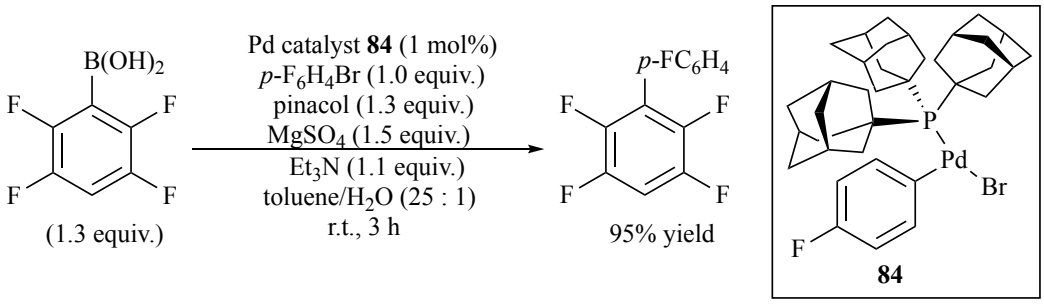
3.0 Conclusions and future work



Scheme 38 Suzuki-Miyaura cross-coupling conditions used in this work.

In this work, iridium/dtbpy-catalysed C-H borylation has proved to be a practical and efficient method for the synthesis of fluorinated aryl and heteroaryl boronic esters. Although isolation and separation of the borylated products remained challenging, tandem C-H borylation/Suzuki-Miyaura cross-coupling sequences were developed to enable the purification of the desired fluorinated biaryls derived from the boronate precursors formed in the initial borylation step. The yields of highly fluorinated biaryl units using procedures containing the aqueous base (Scheme 38a and 38b) were not optimal due to the tendency to protodeboronation in the basic reaction conditions. However, this problem could be potentially addressed by an alternative anhydrous approach, in which fluoride is used to activate the boronic esters in the transmetalation step (Scheme 38c). Exploring the substrate scope of this anhydrous method in

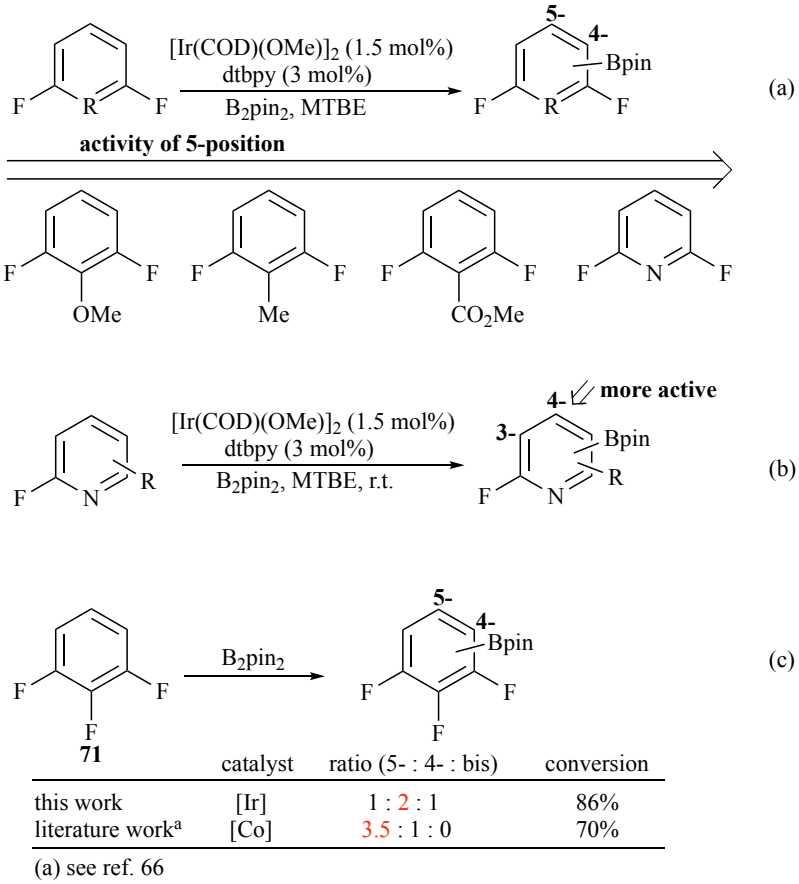
fluorinated boronic esters will be an area for the further work. Other cross-coupling methods of fluorinated boronic acids under weakly basic conditions, for example the use of Pd-based catalyst **84** (Scheme 39)[59] may also offer an alternative solution to this problem.



Scheme 39 A Suzuki-Miyaura cross-coupling condition with no added base.

Through the attempts to explore the regioselectivity and reactivity in the C-H borylation of polyfluoroarenes, some valuable conclusions have been made. With their more electron-deficient nature, fluoroarenes react faster than the equivalent non-fluorinated arenes. For example, whilst the borylation of toluene **9** produced PhMe-Bpin in 30% yield after 16 hours, borylation of 1-fluoro-4-methylbenzene **61** produced 88% yield of borylated product over the same period. Similarly, highly fluorinated substrates are more active than monofluorinated arenes and fluoropyridines are more active than fluoroarenes in C-H borylation reactions. C-H borylation *ortho* to the C-F bonds occurs readily, reflecting the increased C-H acidity at these positions and the low steric size of the fluorine substituent.

With the small steric hindrance of the fluorine atom, site selectivity directed by electronic effects can be clearly observed in the borylation of fluoroarenes. For example, with the increasing electronic-withdrawing ability of the 2-substituent, reactions of 1,3-difluoro-2-substituted arene scaffolds provided more 5-isomers (Scheme 40a). This observation was then reinforced by the borylation of 2-fluoropyridine substrates, which gave a preference for 4-borylated isomers over 3-isomers, even though the 4-position was sometimes more sterically hindered (Scheme 40b).



Scheme 40 Regioselectivity directed by electronic effects in the borylation of 1,3-difluoro-2-substituted arenes.

Whilst a correlation between the electron-withdrawing ability of the 2-substituent and the borylation outcome was established among 1,3-fluoroarene substrates, an exception was found in the reaction of 1,2,3-trifluorobenzene **71**, which exhibited high selectivity for the 4-position (Scheme 40c). This unexpected result was also in contrast to the selectivity reported in literature, in which the 5-position was preferentially activated.[69] The origin of this electronic selectivity has not been well understood, but interpretation of the impact of the fluorine substituent on the regioselectivity for this substrate may be achieved by determination of the carbon-iridium bond energy in the oxidative addition transition state of each borylated isomer using the computational method described by Eisenstein and Perutz.[78]

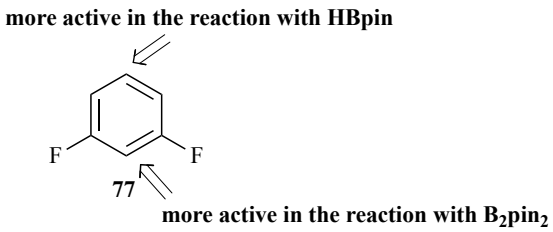


Figure 12 Different selectivity afforded by B_2pin_2 and HBpin in the borylation of **77**.

Time prevented the full study of the regioselectivity of the borylation of 1,3-difluorobenzene **77**. However, the preliminary work in this project showed that in the reaction of **77** with HBpin, the formation of 5-borylated product was favoured, whereas in the reaction with B_2pin_2 the selectivity was variable such that in some cases 2-borylated product was favoured (Figure 12). This latter experiment was challenged by

the fact that the borylation with B_2pin_2 leads to the introduction of HBpin into the reaction mixture. Attempts to sequester HBpin using LiOMe in this reaction were not successful and identifying an alternative method to capture HBpin effectively in the reaction to conform this contrast will be required in the future work. Although preliminary, these results potentially challenged the accepted understanding of the borylation mechanism in which the C-H activation step for both boron reagents proceeds *via* a common catalytically active species. In future investigation, it could be helpful to consider a radical-like intermediate in the reaction with HBpin. This builds on observations suggested by Eisenstein and Perutz[78] that radical formation could result in a regioselectivity that prefers the activation of the weakest C-H bond for which the radical centre is *meta* to a fluorine atom.

4.0 Experimental detail

4.1 General experimental considerations

Handing techniques: Unless otherwise stated, all reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques. Glassware was dried in an oven before use.

Solvents: MTBE was purchased from Fisher Scientific as anhydrous 99% and was degassed before use. All other solvents were dried using Innovative Technology Solvent Purification System (SPS) and stored under nitrogen before use.

Reagents: All reagents were purchased from Sigma Aldrich, Fluorochem, Fisher Scientific, Alfa-Aesar or Apollo Scientific and were used without further purification unless stated.

Chromatography: Thin-layer chromatography (TLC) was carried out on 'Polygram Sil G/UV_{254}' plastic-backed silica plates which were purchased from VWR International. Flash column chromatography was performed using automated system operations by Teledyne Isco CombiFlash on prepacked silica RediSep Rf cartridges.

NMR Spectroscopy: ^{1}H NMR spectra were recorded on a Varian VNMRS-600 at 600 MHz or on a Varian VNMRS-700 at 700 MHz. ^{13}C NMR spectra (proton decoupled) were recorded on a Varian VNMRS-600 at 151 MHz or on a Varian VNMRS-700 at

176 MHz. ^{19}F NMR spectra (proton decoupled) were recorded on a Bruker Avance-400 at 376 MHz. ^{11}B NMR spectra (proton decoupled) were recorded on a Bruker Avance-400 at 128 MHz. All reported ^{1}H and ^{13}C chemical shifts are referenced to the residual signal of deuterated solvents ($CDCl_3$: δ_H = 7.26 ppm, δ_c = 77.16 ppm; DMSO-d_6: δ_H = 2.50 ppm, δ_c = 39.52 ppm). ^{11}B chemical shifts are referenced externally to $BF_3{\cdot}Et_2O$ (δ_B = 0.0 ppm). ^{19}F chemical shifts are referenced externally to $CFCl_3$ (δ_F = 0.0 ppm). Chemical shifts are reported in parts per million (ppm) and coupling constants are reported in Hertz (Hz). Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad signal).

IR Spectroscopy: Infrared spectra were reported on a Perkin-Elmer Paragon 1000 FT-IR Spectrometer with ATR (attenuated total reflection) attachment. Peaks are reported in wavenumber (cm^{-1}).

Melting point: Melting points were recorded using an Electrothermal IA9100 capillary melting point apparatus.

Mass Spectroscopy: Gas chromatography-mass spectrometry (GC-MS) was carried out using a Shimadzu QP2010-Ultra GC-MS spectrometer equipped with a Rxi-5Sil MS column in EI mode. Liquid chromatography-mass spectrometry (LC-MS) was carried out using a TQD mass spectrometer equipped with an Acquity UPLC system. High-resolution mass spectra were obtained on a Q-ToF Premier Mass Spectrometer

with electrospray ionisation (ESI) or atmospheric pressure solids analysis probe (ASAP) on an Acquity LCT premier XE by Durham University Mass Spectrometry Service.

4.2 General procedures

General procedure A (C-H borylation of fluoroarenes)

An oven-dried Biotage microwave vial was sealed and subjected to three N_2 evacuation/refill cycles, followed by the addition of the corresponding fluoroarene (1.00 mmol, 1.0 equiv.). In a separate oven-dried Schlenk tube was charged with $[Ir(COD)(OMe)]_2$ (9.9 mg, 1.5 mol%), dtbpy (8.1 mg, 3.0 mol%), and bis(pinacolato)diboron (B_2pin_2) (0.6 equiv. to 1.5 equiv.). The vessel was sealed and subjected to three N_2 evacuation/refill cycles before anhydrous MTBE (1.0 mL) was added. Once the solids were completely dissolved, this black active catalyst solution was transferred into the microwave vial using a syringe. The reaction was stirred at room temperature/60 ℃ before being monitored by ^{19}F NMR or GC-MS. Upon completion, the volatiles were then removed *in vacuo* and the desired borylated product was isolated following purification by flash column chromatography with the appropriate solvent system.

General procedure B (Suzuki-Miyaura cross-coupling reactions of fluorinated boronic esters)

General procedure B1

To a microwave vial which contained the substrate boronic ester (1.0 equiv.) was added

$Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (2.5 mol%), K_3PO_4 (1.5-2.0 equiv.), and methyl 4-iodobenzoate (1.0 equiv.) in DMAc (1 mL). The reaction mixture was degassed using a nitrogen filled balloon and stirred at room temperature/80 ℃. Once judged complete by ^{19}F NMR, the reaction was diluted with EtOAc (20 mL) and washed with water (2×10 mL) and brine (10 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The cross-coupled arene was then purified by flash column chromatography with the appropriate solvent system.

General procedure B2

To a microwave vial which contained the substrate boronic ester (1.0 equiv.) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (2.5 mol%) and K_3PO_4 (1.5 equiv.). The vial was sealed and subjected to three N_2 evacuation/refill cycles before the aryl halide (1.0 equiv.) and pre-degassed solvent DMAc (1 mL) were added. The reaction mixture was stirred at room temperature. Once judged complete by ^{19}F NMR, the reaction was diluted with EtOAc (20 mL) and washed with water (2×10 mL) and brine (10 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The cross-coupled arene was then purified by flash column chromatography with the appropriate solvent system.

General procedure B3

To a microwave vial which contained the substrate boronic ester (1.0 equiv.) was added $Pd_2(dba)_3$ (5 mol%), CsF (2.0 equiv.), $P(t\text{-}Bu)_3 \cdot HBF_4$ (10 mol%), and CuCl (2.0 equiv.).

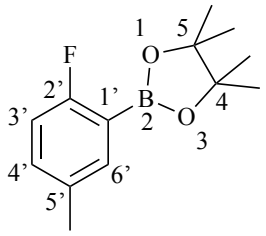
The vial was sealed and subjected to three N_2 evacuation/refill cycles before the aryl halide (1.0 equiv.) and dry solvent DMF (1 mL) were added. The reaction mixture was stirred at 100 ℃. Once judged complete by ^{19}F NMR, the reaction was diluted with EtOAc (20 mL) and washed with water (2×10 mL) and brine (10 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The cross-coupled arene was then purified by flash column chromatography with the appropriate solvent system.

General procedure B4

To a microwave vial which contained the substrate boronic ester (1.0 equiv.) was added $Pd(dppf)Cl_2$ (10 mol%) and tetra-*n*-butylammonium bromide (TBAB, 10 mol%). The vial was sealed and subjected to three N_2 evacuation/refill cycles before the aryl halide (1.5 equiv.) and pre-degassed dry toluene were added. The mixture was then cooled to 0 ℃ and 2M aq. Na_2CO_3 (2 equiv.) was added dropwise. The reaction mixture was stirred at 110 ℃. Once judged complete by ^{19}F NMR, the resulting solution was filtered through celite, washed with DCM, and concentrated *in vacuo*. The cross-coupled arene was then purified by flash column chromatography with the appropriate solvent system.

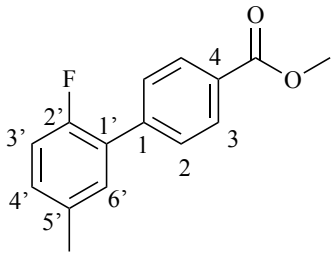
4.3 Experimental details

61a: 2-(2-fluoro-5-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



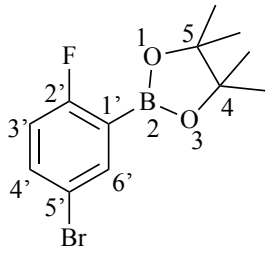
General procedure A was applied to 1-fluoro-4-methylbenzene (0.11 mL, 1.00 mmol, 1.0 equiv.) and B_2pin_2 (253.9 mg, 1.00 mmol, 1.0 equiv.) at room temperature with a reaction time of 24 h. Flash column chromatography (0-100% EtOAc in hexane) afforded the desired borylated product **61a** as a colourless oil (43.0 mg, 0.18 mmol, 18%). ν_{max} (ATR) 2934, 1618, 1496, 1410, 1349, 1219, 1146, 1072, 967, 854, 824, 737, 707, 661, 528 cm $^{-1}$; δ_H (700 MHz, $CDCl_3$) 7.53 (1H, dd, *J* = 5.8, 2.5 Hz, 6'-*H*), 7.23 ~ 7.19 (1H, m, 4'-*H*), 6.91 (1H, t, *J* = 8.8 Hz, 3'-*H*), 2.31 (3H, s, 5'-C*H*$_3$), 1.36 (12H, s, 4-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 165.6 (d, *J* = 250 Hz, C-2'), 137.0 (d, *J* = 8 Hz, C-6'), 133.9 (d, *J* = 9 Hz, C-4'), 132.9 (d, *J* = 3 Hz, C-5'), 115.1 (d, *J* = 25 Hz, C-3'), 84.0 (s, C-4), 24.9 (s, $OCCH_3$), 20.5 (s, 5'-CH_3); δ_F (376 MHz, $CDCl_3$) -108.3 (1F, s); δ_B (128 MHz, $CDCl_3$) 30.2; HRMS (ASAP) m/z found $[M+H]^+$ 236.1485, $C_{13}H_{19}{}^{10}BFO_2$ requires *M*, 236.1498. Data for this compound were consistent with previous reports.[79]

61c: methyl 2'-fluoro-5'-methyl-[1,1'-biphenyl]-4-carboxylate



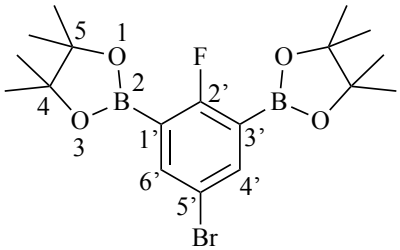
General procedure A [1-fluoro-4-methylbenzene (0.11 mL, 1.00 mmol, 1.0 equiv.), B_2pin_2 (152.4 mg, 0.60 mmol, 0.6 equiv.), 81% conversion (**61a** : **61b** = 4 : 1) at 60 °C after 1 h] and B1 [Pd(dppf)Cl_2·CH_2Cl_2 (20.4 mg, 2.5 mol%), K_3PO_4 (424.5 mg, 2.00 mmol, 2.0 equiv.) and methyl 4-iodobenzoate (262.0 mg, 1.00 mmol, 1.0 equiv.) at 80 °C for 18 h] were applied in a one-pot protocol. Flash column chromatography (20-30% Et_2O in hexane) afforded the desired cross-coupled arene **61c** as a white solid (90.1 mg, 0.37 mmol, 37%). M.p. 54.8-55.7 °C; ν_{max} (ATR) 2993, 2960, 1723, 1615,1497,1441, 1116, 896, 736, 706 cm $^{-1}$; δ_H (599 MHz, $CDCl_3$) 8.10 (2H, d, *J* = 8.4 Hz, 3-*H*), 7.61 (2H, dd, *J* = 8.4, 1.7 Hz, 2-*H*), 7.24 (1H, dd, *J* = 7.6, 2.3 Hz, 6'-*H*), 7.14 (1H, ddd, *J* = 7.6, 4.8, 2.3 Hz, 4'-*H*), 7.05 (1H, dd, *J* = 10.5, 8.3 Hz, 3'-*H*), 3.94 (3H, s, OCH_3), 2.37 (3H, s, 5'-CH_3); δ_C (151 MHz, $CDCl_3$) 167.0 (s, C=O), 158.1 (d, *J* = 246 Hz, C-2'), 140.7 (d, *J* = 1 Hz, C-1), 134.0 (d, *J* = 4 Hz, C-5'), 131.1 (d, *J* = 3 Hz, C-6'), 130.3 (d, *J* = 8 Hz, C-4'), 129.8 (s, C-3), 129.2 (s, C-4), 129.1 (d, *J* = 3 Hz, C-2), 127.6 (d, *J* = 13 Hz, C-1'), 116.0 (d, *J* = 23 Hz, C-3'), 52.2 (s, OCH_3), 20.8 (s, 5'-CH_3); δ_F (376 MHz, $CDCl_3$) -122.9 (1F, s); HRMS (ASAP) m/z found $[M+H]^+$ 245.0988, $C_{15}H_{14}FO_2$ requires *M*, 245.0978. Data for this compound were consistent with previous reports.[80]

62a: 2-(5-bromo-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



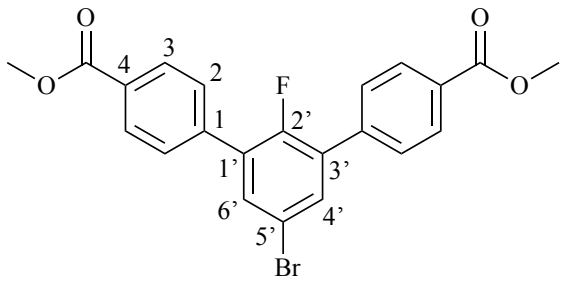
General procedure A was applied to 1-bromo-4-fluorobenzene (0.11 mL, 1.00 mmol, 1.0 equiv.) and B_2pin_2 (152.4 mg, 0.60 mmol, 0.6 equiv.) at room temperature with a reaction time of 4 h. Flash column chromatography (0-100% EtOAc in toluene) afforded the desired borylated product **62a** as a colourless oil (41.8 mg, 0.14 mmol, 14%). ν_{max} (ATR) 2944, 1611, 1483, 1405, 1336, 1221, 1144, 1083, 963, 868, 851, 823, 735, 706, 678, 621 cm $^{-1}$; δ_H (700 MHz, $CDCl_3$) 7.83 (1H, dd, *J* = 5.1, 2.7 Hz, 6'-*H*), 7.51 (1H, ddd, *J* = 8.8, 4.8, 2.7 Hz, 4'-*H*), 6.92 (1H, t, *J* = 8.8 Hz, 3'-*H*), 1.36 (12H, s, 4-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 166.2 (d, *J* = 252 Hz, C-2'), 139.4 (d, *J* = 8 Hz, C-6'), 136.1 (d, *J* = 9 Hz, C-4'), 117.5 (d, *J* = 26 Hz, C-3'), 116.6 (d, *J* = 3 Hz, C-5'), 84.4 (s, C-4), 25.0 (s, CH_3); δ_F (376 MHz, $CDCl_3$) -105.3 (1F, s); δ_B (128 MHz, $CDCl_3$) 29.7; HRMS (ASAP) m/z found $[M]^+$ 299.0369, $C_{12}H_{15}{}^{10}B^{79}BrFO_2$ requires *M*, 299.0369.

62b: 2,2'-(5-bromo-2-fluoro-1,3-phenylene)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)



General procedure A was applied to 1-bromo-4-fluorobenzene (0.11 mL, 1.00 mmol, 1.0 equiv.) and B_2pin_2 (304.7 mg, 1.20 mmol, 1.2 equiv.) at 60 ℃ with a reaction time of 17 h. Flash column chromatography (0-20% MeOH in DCM) afforded the desired borylated product **62b** as a light-yellow oil (260.4 mg, 0.61 mmol, 61%). ν_{max} (ATR) 2944, 1608, 1425, 1380, 1318, 1216, 1140, 969, 898, 850, 735, 705 cm $^{-1}$; δ_H (700 MHz, $CDCl_3$) 7.89 (2H, d, J = 4.9 Hz, 4'-H), 1.32 (24H, s, 4-CH_3); δ_C (176 MHz, $CDCl_3$) 170.4 (d, J = 256 Hz, C-2'), 142.4 (d, J = 9 Hz, C-4'), 117.4 (d, J = 26 Hz, C-1'), 116.6 (d, J = 3 Hz, C-5'), 84.3 (s, C-4), 24.9 (s, CH_3); δ_F (376 MHz, $CDCl_3$) -94.8 (1F, s); δ_B (128 MHz, $CDCl_3$) 29.6; HRMS (ASAP) m/z found $[M]^+$ 424.1271, $C_{18}H_{26}{}^{10}B_2{}^{79}BrFO_4$ requires M, 424.1257.

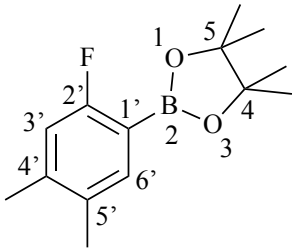
62c: dimethyl 5'-bromo-2'-fluoro-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate



General procedure A [1-bromo-4-fluorobenzene (0.11 mL, 1.00 mmol, 1.0 equiv.), B_2pin_2 (152.4 mg, 0.60 mmol, 0.6 equiv.), 84% conversion (**62a** : **62b** = 4.5 : 1) at room temperature after 3 h] and B1 [Pd(dppf)Cl_2·CH_2Cl_2 (20.4 mg, 2.5 mol%), K_3PO_4 (424.5 mg, 2.00 mmol, 2.0 equiv.) and methyl 4-iodobenzoate (262.0 mg, 1.00 mmol, 1.0 equiv.) at 80 ℃ for 1h] were applied in a one-pot protocol. Flash column chromatography (0-20% Et_2O in toluene) afforded the desired cross-coupled arene **62c**

as a white solid (29.3 mg, 0.07 mmol, 7%). ν_{max} (ATR) 2992, 2963, 1729, 1614, 1443, 1114, 1017, 899, 855, 803, 733, 704 cm $^{-1}$; δ_H (700 MHz, $CDCl_3$) 8.13 (4H, d, *J* = 8.5 Hz, 3-*H*), 7.62 (4H, d, *J* = 8.5 Hz, 2-*H*), 7.59 (2H, d, *J* = 6.2 Hz, 4'-*H*), 3.95 (6H, s, OC*H*$_3$); δ_C (176 MHz, $CDCl_3$) 166.8 (s, C=O), 155.7 (d, *J* = 252 Hz, C-2'), 139.0 (s, C-1), 133.1 (d, *J* = 3 Hz, C-4'), 131.0 (d, *J* = 16 Hz, C-3'), 130.1 (s, C-4), 130.0 (s, C-3), 129.3 (d, *J* = 3 Hz, C-2), 117.3 (d, *J* = 4 Hz, C-5'), 52.4 (s, OCH_3); δ_F (376 MHz, $CDCl_3$) -124.1 (1F, s); HRMS (ASAP) m/z found $[M]^+$ 442.0237, $C_{22}H_{16}{}^{79}BrFO_4$ requires *M*, 442.0216.

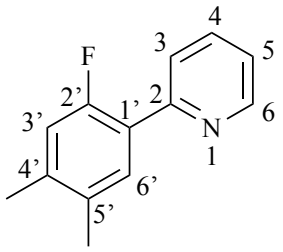
64a: 2-(2-fluoro-4,5-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



General procedure A was applied to 4-fluoro-1,2-dimethylbenzene (0.12 mL, 1.00 mmol, 1.0 equiv.) and B_2pin_2 (304.7 mg, 1.20 mmol, 1.2 equiv.) at 60 °C with a reaction time of 1 h. Flash column chromatography (0-20% EtOAc in toluene) afforded the desired borylated product **64a** as a colourless oil (162.7 mg, 0.65 mmol, 65%). ν_{max} (ATR) 2923, 1632, 1406, 1377, 1346, 1140, 1033, 899, 861, 735, 706 cm $^{-1}$; δ_H (700 MHz, $CDCl_3$) 7.47 (1H, d, *J* = 6.2 Hz, 6'-*H*), 6.82 (1H, d, *J* = 10.0 Hz, 3'-*H*), 2.25 (3H, s, 4'-C*H*$_3$), 2.21 (3H, s, 5'-C*H*$_3$), 1.36 (12H, s, 4-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 165.8 (d, *J* = 249 Hz, C-2'), 142.7 (d, *J* = 9 Hz, C-4'), 137.4 (d, *J* = 8 Hz, C-6'), 131.7 (d, *J* = 3

Hz, C-5'), 116.3 (d, J = 24 Hz, C-3'), 112.6 (br s, C-1'), 83.7 (s, C-4), 24.9 (s, $OCCH_3$), 20.2 (d, J = 2 Hz, 4'-CH_3), 18.7 (s, 5'-CH_3); δ_F (376 MHz, $CDCl_3$) -108.2 (1F, s); δ_B (128 MHz, $CDCl_3$) 30.2; HRMS (ASAP) m/z found $[M+H]^+$ 250.1647, $C_{14}H_{21}{}^{10}BFO_2$ requires M, 250.1655.

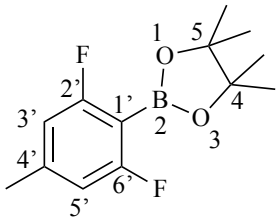
64b: 2-(2-fluoro-4,5-dimethylphenyl)pyridine



General procedure B1 was applied to **64a** (131.2 mg, 0.53 mmol, 1.00 equiv.), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10.7 mg, 2.5 mol%), K_3PO_4 (222.9 mg, 1.05 mmol, 2.0 equiv.) and 2-bromopyridine (0.05 mL, 0.53 mmol, 1.00 equiv.) at 80 °C with a reaction time of 19 h. Flash column chromatography (20-30% Et_2O in hexane) afforded the desired cross-coupled arene **64b** as an oily light yellow solid (35.7 mg, 0.18 mmol, 34%). ν_{max} (ATR) 2929, 2864, 1631, 1594, 1509, 1468, 1185, 1133, 1018, 901, 857, 782, 733, 703 cm $^{-1}$; δ_H (599 MHz, DMSO) 8.72 (1H, ddd, J = 4.8, 1.8, 0.9 Hz, 6-H), 7.96 (1H, td, J = 7.8, 1.8 Hz, 4-H), 7.82 ~ 7.78 (1H, m, 3-H), 7.71 (1H, d, J = 8.2 Hz, 6'-H), 7.44 (1H, ddd, J = 7.8, 4.8, 1.1 Hz, 5-H), 7.14 (1H, d, J = 12.2 Hz, 3'-H), 2.28 (3H, s, 4'-CH_3), 2.26 (3H, s, 5'-CH_3); δ_C (151 MHz, DMSO) 157.9 (d, J = 245.9 Hz, C-2'), 151.9 (d, J = 2.2 Hz, C-1'), 148.8 (s, C-6), 140.1 (d, J = 8.4 Hz, C-4'), 137.9 (s, C-4), 132.6 (d, J = 3.2 Hz, C-5'), 131.1 (d, J = 3.1 Hz, C-6'), 124.3 (d, J = 8.6 Hz, C-3), 122.9 (s, C-5),

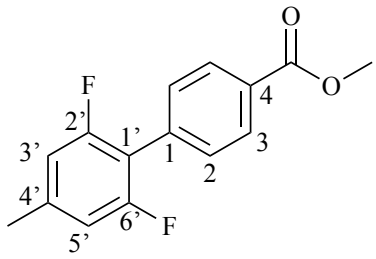
122.8 (s, C-2), 116.9 (d, J = 22.4 Hz, C-3'), 19.2 (d, J = 1.2 Hz, 4'-CH_3), 18.5 (s, 5'-CH_3); δ_F (376 MHz, DMSO) -122.3 (1F, s); HRMS (ESI) m/z found $[M+H]^+$ 202.1021, $C_{13}H_{13}FN$ requires M, 202.1032.

66a: 2-(2,6-difluoro-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



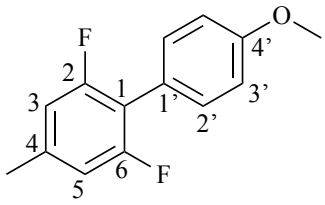
General procedure A was applied to 1, 3-difluoro-5-methylbenzene (0.11 mL, 1.00 mmol, 1.0 equiv.) and B_2pin_2 (304.7 mg, 1.20 mmol, 1.2 equiv.) at 60 °C with a reaction time of 1.5 h. Flash column chromatography (0-15% Et_2O in hexane) afforded the desired borylated product **66a** as a white solid (181.3 mg, 0.71 mmol, 71%). M.p. 56.1-57.5 °C; ν_{max} (ATR) 2991, 1637, 1426, 1350, 1139, 1075, 899, 733, 706 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 6.64 (2H, d, J = 8.1 Hz, 3'-H), 2.31 (3H, s, 4'-CH_3), 1.36 (12H, s, 4-CH_3); δ_C (176 MHz, $CDCl_3$) 166.8 (dd, J = 250, 14 Hz, C-2'), 144.8 (t, J = 11 Hz, C-4'), 111.8 (dd, J = 23, 4 Hz, C-3'), 84.1 (s, C-4), 24.8 (s, $OCCH_3$), 21.6 (s, 4'-CH_3); δ_F (376 MHz, $CDCl_3$) -101.7 (2F, s); δ_B (128 MHz, $CDCl_3$) 29.7; HRMS (ASAP) m/z found $[M+H]^+$ 254.1419, $C_{13}H_{18}{}^{10}BF_2O_2$ requires M, 254.1404. Data for this compound were consistent with previous reports.[81]

66b: methyl 2',6'-difluoro-4'-methyl-[1,1'-biphenyl]-4-carboxylate



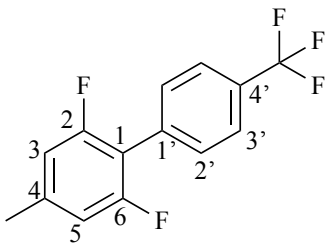
General procedure B1 was applied to **66a** (127.0 mg, 0.50 mmol, 1.00 equiv.), Pd(dppf)Cl_2·CH_2Cl_2 (10.2 mg, 2.5 mol%), K_3PO_4 (159.2 mg, 0.75 mmol, 1.5 equiv.) and methyl 4-iodobenzoate (131.0 mg, 0.50 mmol, 1.00 equiv.) at room temperature with a reaction time of 4 h. Flash column chromatography (25-30% chloroform in hexane) afforded the desired cross-coupled arene **66b** as a white solid (143.7 mg, 0.27 mmol, 55%). M.p. 98.7-99.3 °C; ν_{max} (ATR) 2994, 1726, 1644, 1439, 1424, 1115, 1040, 894, 733, 705 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.11 (2H, d, *J* = 8.6 Hz, 3-*H*), 7.53 (2H, d, *J* = 8.6 Hz, 2-*H*), 6.81 (2H, d, *J* = 8.3 Hz, 3'-*H*), 3.94 (3H, s, OCH_3), 2.38 (3H, s, 4'-CH_3); δ_C (176 MHz, $CDCl_3$) 166.9 (s, C=O), 159.8 (dd, *J* = 249, 8 Hz, C-2'), 141.0 (t, *J* = 10 Hz, C-4'), 134.4 (s, C-1), 130.5 (t, *J* = 2 Hz, C-2), 129.7 (s, C-4), 129.5 (s, C-3), 114.6 (t, *J* = 19 Hz, C-1'), 112.5 (dd, *J* = 22, 4 Hz, C-3'), 52.3 (s, OCH_3), 21.4 (s, 4'-CH_3); δ_F (376 MHz, $CDCl_3$) -115.5 (2F, s); HRMS (ESI) m/z found $[M+H]^+$ 263.0883, $C_{15}H_{13}F_2O_2$ requires *M*, 263.0884.

66c: 2,6-difluoro-4'-methoxy-4-methyl-1,1'-biphenyl



General procedure B1 was applied to **66a** (127.0 mg, 0.50 mmol, 1.00 equiv.), Pd(dppf)Cl_2·CH_2Cl_2 (10.2 mg, 2.5 mol%), K_3PO_4 (159.2 mg, 0.75 mmol, 1.5 equiv.) and 1-iodo-4-methoxybenzene (117.0 mg, 0.50 mmol, 1.00 equiv.) at room temperature with a reaction time of 4 h. Flash column chromatography (15-20% chloroform in hexane) afforded the desired cross-coupled arene **66c** as a white solid (55.7 mg, 0.24 mmol, 48%). M.p. 68.7-69.2 °C; ν_{max} (ATR) 2993, 2689, 2308, 1424, 1323, 1206, 1185, 1040, 898, 732, 706 cm^{-1}; δ_H (599 MHz, $CDCl_3$) 7.40 (2H, d, *J* = 8.8 Hz, 2'-*H*), 6.99 (2H, d, *J* = 8.8 Hz, 3'-*H*), 6.79 (2H, d, *J* = 8.2 Hz, 3-*H*), 3.85 (3H, s, OCH_3), 2.37 (3H, s, 4-CH_3); δ_C (151 MHz, $CDCl_3$) 160.0 (dd, *J* = 246, 8 Hz, C-2), 159.4 (s, C-4'), 139.5 (t, *J* = 10 Hz, C-4), 131.6 (s, C-2'), 121.7 (s, C-1'), 115.2 (t, *J* = 19 Hz, C-1), 113.9 (s, C-3'), 112.3 (dd, *J* = 21, 5 Hz, C-3), 55.4 (s, OCH_3), 21.4 (s, 4-CH_3); δ_F (376 MHz, $CDCl_3$) -116.0 (2F, s); HRMS (ASAP) m/z found $[M]^+$ 234.0860, $C_{14}H_{12}F_2O$ requires *M*, 234.0856.

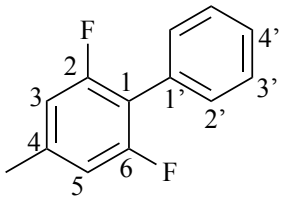
66d: 2,6-difluoro-4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl



General procedure B2 was applied to **66a** (127.0 mg, 0.50 mmol, 1.00 equiv.), Pd(dppf)Cl_2·CH_2Cl_2 (10.2 mg, 2.5 mol%), K_3PO_4 (159.2 mg, 0.75 mmol, 1.5 equiv.) and 1-iodo-4-(trifluoromethyl)benzene (0.07 mL, 0.50 mmol, 1.00 equiv.) at room

temperature with a reaction time of 4 h. Flash column chromatography (0-5% chloroform in hexane) afforded the desired cross-coupled arene **66d** as a white solid (84.0 mg, 0.31 mmol, 62%). M.p. 68.5-69.2 °C; ν_{max} (ATR) 2993, 2312, 1643, 1426, 1327, 1204, 1173, 1073, 894, 846, 733, 706 cm^{-1}; δ_H (599 MHz, $CDCl_3$) 7.70 (2H, d, *J* = 8.2 Hz, 3'-*H*), 7.58 (2H, d, *J* = 8.0 Hz, 2'-*H*), 6.84 (2H, d, *J* = 8.4 Hz, 3-*H*), 2.40 (3H, s, 4-C*H*$_3$); δ_C (151 MHz, $CDCl_3$) 159.8 (dd, *J* = 249, 8 Hz, C-2), 141.2 (t, *J* = 10 Hz, C-4), 133.4 (s, C-1'), 130.9 (t, *J* = 2 Hz, C-2'), 130.2 (q, *J* = 33 Hz, C-4'), 125.3 (q, *J* = 4 Hz, C-3'), 124.3 (br q, *J* = 272 Hz, CF_3), 114.2 (t, *J* = 19 Hz, C-1), 112.5 (dd, *J* = 21, 5 Hz, C-3), 21.5 (s, CH_3); δ_F (376 MHz, $CDCl_3$) -62.7 (3F, s, CF_3), -115.84 (2F, s, F-2); HRMS (ASAP) m/z found $[M]^+$ 272.0626, $C_{14}H_9F_5$ requires *M*, 272.0624.

66e: 2,6-difluoro-4-methyl-1,1'-biphenyl

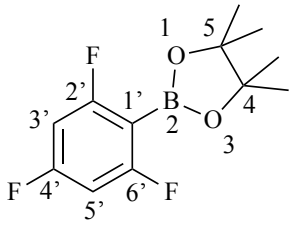


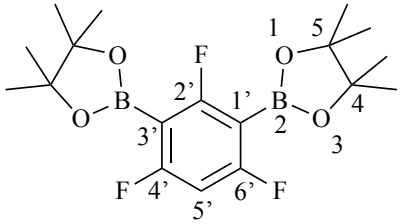
General procedure B2 was applied to **66a** (127.0 mg, 0.50 mmol, 1.00 equiv.), Pd(dppf)Cl_2·CH_2Cl_2 (10.2 mg, 2.5 mol%), K_3PO_4 (159.2 mg, 0.75 mmol, 1.5 equiv.) and iodobenzene (0.06 mL, 0.50 mmol, 1.00 equiv.) at room temperature with a reaction time of 4 h. Flash column chromatography (0-5% chloroform in hexane) afforded the desired cross-coupled arene **66e** as a white solid (68.9 mg, 0.34 mmol, 68%). M.p. 79.6-80.0 °C; ν_{max} (ATR) 2994, 2685, 2313, 1645, 1425, 1321, 1203, 1040, 897, 732, 706 cm^{-1}; δ_H (599 MHz, $CDCl_3$) 7.50 ~ 7.37 (5H, m, 2', 3', 4'-*H*), 6.82 (2H,

d, J = 8.2 Hz, 3-H), 2.39 (3H, s, CH_3); δ_C (151 MHz, $CDCl_3$) 160.0 (dd, J = 248, 8 Hz, C-2), 140.0 (t, J = 10 Hz, C-4), 130.5 (t, J = 2 Hz, C-2'), 129.6 (s, C-1'), 128.3 (s, C-4'), 128.1 (s, C-3'), 115.6 (t, J = 19 Hz, C-1), 112.3 (dd, J = 21, 5 Hz, C-3), 21.4 (s, CH_3); δ_F (376 MHz, $CDCl_3$) -115.8 (2F, s); HRMS (ASAP) m/z found $[M]^+$ 204.0751, $C_{13}H_{10}F_2$ requires M, 204.0751.

67a: 4,4,5,5-tetramethyl-2-(2,4,6-trifluorophenyl)-1,3,2-dioxaborolane

67b: 2,2'-(2,4,6-trifluoro-1,3-phenylene)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)

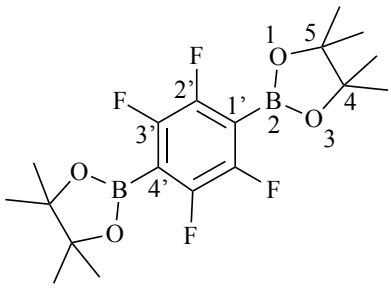




General procedure A was applied to 1, 3, 5-trifluorobenzene (0.10 mL, 1.00 mmol, 1.0 equiv.) and B_2pin_2 (152.4 mg, 0.60 mmol, 0.6 equiv.) at room temperature with a reaction time of 2 h. Flash column chromatography (0-20% MeOH in DCM) afforded a mixture of two borylated products (**67a** and **67b**) as a colourless oil (128.8 mg, 0.50 mmol, 50%, ratio by ^{19}F NMR was 98 : 2). **67a**: δ_H (599 MHz, $CDCl_3$) 6.63 ~ 6.58 (2H, m, 3'-H), 1.37 (12H, s, 4-CH_3); δ_C (151 MHz, $CDCl_3$) 167.5 (dt, J = 252, 16 Hz, C-2'), 165.3 (dt, J = 252, 16 Hz, C-4'), 100.5 ~ 100.0 (m, C-3'), 84.4 (s, C-4), 24.9 (s, CH_3); δ_F (376 MHz, $CDCl_3$) -97.2 (2F, dd, J = 9, 3 Hz), -103.9 (1F, t, J = 9 Hz); δ_B (128 MHz, $CDCl_3$) 29.4; HRMS (ASAP) m/z found $[M+H]^+$ 258.1144, $C_{12}H_{15}{}^{10}BF_3O_2$ requires M,

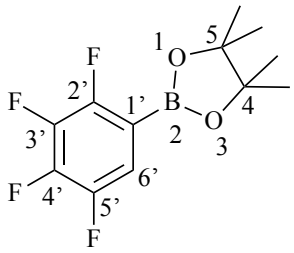
258.1154. Data for this compound were consistent with previous reports.[82] **67b**: δ_H (599 MHz, $CDCl_3$) 6.63 ~ 6.58 (1H, m, 5'-*H*), 1.35 (24H, s, 4-C*H*$_3$); δ_C (151 MHz, $CDCl_3$) 100.5 ~ 100.0 (m, C-5'), 84.3 (s, C-4), 24.7 (s, CH_3); δ_F (376 MHz, $CDCl_3$) -86.4 (1F, t, *J* =7 Hz), -93.8 (2F, dd, *J* =7, 2 Hz); δ_B (128 MHz, $CDCl_3$) 29.4; HRMS (ASAP) m/z found $[M+H]^+$ 383.2067, $C_{18}H_{26}{}^{10}B_2F_3O_4$ requires *M*, 383.2042.

68b: 2,2'-(perfluoro-1,4-phenylene)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)



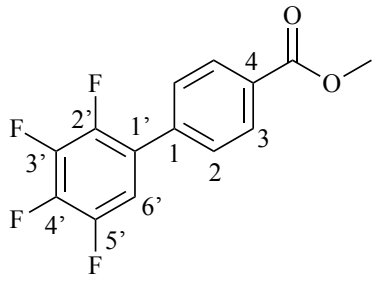
General procedure A was applied to 1, 2, 4, 5-tetrafluorobenzene (0.10 mL, 1.00 mmol, 1.0 equiv.) and B_2pin_2 (304.7 mg, 1.20 mmol, 1.2 equiv.) at 60 °C with a reaction time of 3 h. Flash column chromatography (0-20% EtOAc in toluene) afforded the desired borylated product **68b** as a white solid (335.0 mg, 0.83 mmol, 83%). M.p. 185.1-186.0 °C; ν_{max} (ATR) 2939, 1457, 1347, 1208, 1139, 963, 873, 845, 736, 720, 705 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 1.37 (24H, s, 4-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 148.6 (dm, *J* = 254 Hz, C-2'), 111.0 (br s, C-1'), 85.0 (s, C-4), 24.8 (s, $OCCH_3$); δ_F (376 MHz, $CDCl_3$) -131.4 (4F, s); δ_B (128 MHz, $CDCl_3$) 29.1; HRMS (ASAP) m/z found $[M]^+$ 400.1859, $C_{18}H_{24}{}^{10}B_2F_4O_4$ requires *M*, 400.1869.

69a: 4,4,5,5-tetramethyl-2-(2,3,4,5-tetrafluorophenyl)-1,3,2-dioxaborolane



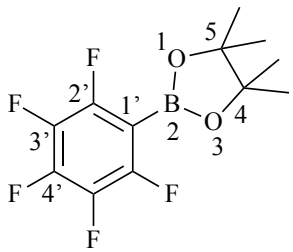
General procedure A was applied to 1, 2, 3, 4-tetrafluorobenzene (0.11 mL, 1.00 mmol, 1.0 equiv.) and B_2pin_2 (304.7 mg, 1.20 mmol, 1.2 equiv.) at room temperature with a reaction time of 30 min. Flash column chromatography (0-100% EtOAc in hexane) afforded the desired borylated product **69a** as a white solid (115.7 mg, 0.42 mmol, 42%). M.p. 42.5-43.8 °C; ν_{max} (ATR) 2942, 1646, 1474, 1419, 1392, 1250, 1146, 1098, 1023, 965, 894, 734, 703, 614 cm $^{-1}$; δ_H (700 MHz, $CDCl_3$) 7.32 ~ 7.28 (1H, m, 6'-*H*), 1.35 (12H, s, 4-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 151.7 (dm, *J* = 250, Hz, C-2'), 147.1 (ddd, *J* = 248, 10, 3 Hz, C-5'), 142.7 (dm, *J* = 257 Hz, C-4'), 140.7 (dm, *J* = 256 Hz, C-3'), 116.7 (ddd, J = 18, 8, 4 Hz, C-6'), 112.4 (br s, C-1'), 84.8 (s, C-4), 24.9 (s, CH_3); δ_F (376 MHz, $CDCl_3$) -129.0 (1F, ddd, *J* = 20, 15, 7 Hz, F-2'), -139.8 (1F, ddd, *J* = 20, 15, 2 Hz, F-5'), -150.9 (1F, td, *J* = 20, 7 Hz, F-4'), -156.1 (1F, t, *J* = 20 Hz, F-3'); δ_B (128 MHz, $CDCl_3$) 29.4; HRMS (ESI) m/z found $[M+H]^+$ 276.1048, $C_{12}H_{14}{}^{10}BF_4O_2$ requires *M*, 276.1059.

69b: methyl 2',3',4',5'-tetrafluoro-[1,1'-biphenyl]-4-carboxylate



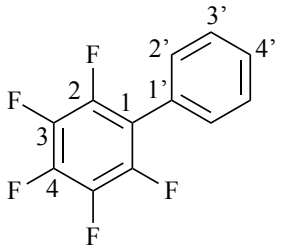
General procedure A [1, 2, 3, 4-tetrafluorobenzene (0.11 mL, 1.00 mmol, 1.0 equiv.), B_2pin_2 (304.7 mg, 1.20 mmol, 1.2 equiv.), 98% conversion at 60 ℃ after 1 h] and B1 [$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (20.4 mg, 2.5 mol%), K_3PO_4 (318.4 mg, 1.50 mmol, 1.5 equiv.) and methyl 4-iodobenzoate (262.0 mg, 1.00 mmol, 1.0 equiv.) at 80 ℃ for 2.5 h] were applied in a one-pot protocol. Flash column chromatography (0-5% Et_2O in hexane) afforded the desired cross-coupled arene **69b** as a white solid (101.2 mg, 0.36 mmol, 36%). M.p. 124.8-125.6 ℃; ν_{max} (ATR) 2941, 1425, 1346, 1189, 1004, 894, 733, 704 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 8.12 (2H, d, *J* = 8.6 Hz, 3-*H*), 7.55 (2H, dd, *J* = 8.6, 1.5 Hz, 2-*H*), 7.11 ~ 7.06 (1H, m, 6'-*H*), 3.95 (3H, s, $OC\mathit{H}_3$); δ_C (176 MHz, $CDCl_3$) 166.6 (s, C=O), 147.3 (dd, *J* = 248, 11 Hz, C-5'), 145.1 (ddd, *J* = 250, 11, 3 Hz, C-2'), 141.4 (dddd, *J* = 254, 17, 12, 4 Hz, C-4'), 140.4 (dddd, *J* = 255, 16, 13, 3 Hz, C-3'), 137.6 (s, C-1), 130.5 (s, C-4), 130.2 (s, C-3), 129.0 (d, *J* = 3 Hz, C-2), 124.5 (ddd, *J* = 12, 7, 4 C-1'), 111.5 (dt, *J* = 20, 3 Hz, C-6'), 52.4 (s, OCH_3); δ_F (376 MHz, $CDCl_3$) -138.9 (1F, ddd, *J* = 20, 13, 3, F-5'), -143.0 (1F, ddd, *J* = 20, 13, 3, F-2'), -154.5 (1F, t, *J* = 20 Hz, F-4'), -155.5 (1F, t, *J* = 20 Hz, F-3'); HRMS (ASAP) m/z found $[M]^+$ 284.0466, $C_{14}H_8F_4O_2$ requires *M*, 284.0460.

70a: 4,4,5,5-tetramethyl-2-(perfluorophenyl)-1,3,2-dioxaborolane



General procedure A was applied to 1, 2, 3, 4, 5-pentafluorobenzene (0.11 mL, 1.00 mmol, 1.0 equiv.) and B_2pin_2 (304.7 mg, 1.20 mmol, 1.2 equiv.) at room temperature with a reaction time of 2 h. Flash column chromatography (0-15% Et_2O in hexane) afforded the desired borylated product **70a** as a colourless oil (181.7 mg, 0.62 mmol, 62%). ν_{max} (ATR) 2892, 2309, 2258, 1656, 1491, 1357, 1142, 982, 911, 731, 706 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 1.36 (12H, s, 4-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 149.4 (dm, *J* = 250 Hz, C-2'), 143.1 (dm, *J* = 256 Hz, C-4'), 137.4 (dm, *J* = 251 Hz, C-3'), 102.9 (br s, C-1'), 85.1 (s, C-4), 24.7 (s, $OCCH_3$); δ_F (376 MHz, $CDCl_3$) -129.4 ~ -129.6 (2F, m, F-2'), -149.8 (1F, t, *J* = 20 Hz, F-4'), -162.0 (2F, td, *J* = 21, 9 Hz, F-3'); δ_B (128 MHz, $CDCl_3$) 29.0; HRMS (ASAP) m/z found $[M+H]^+$ 294.0969, $C_{12}H_{13}{}^{10}BF_5O_2$ requires *M*, 294.0965. Data for this compound were consistent with previous reports.[83]

70b: 2,3,4,5,6-pentafluoro-1,1'-biphenyl



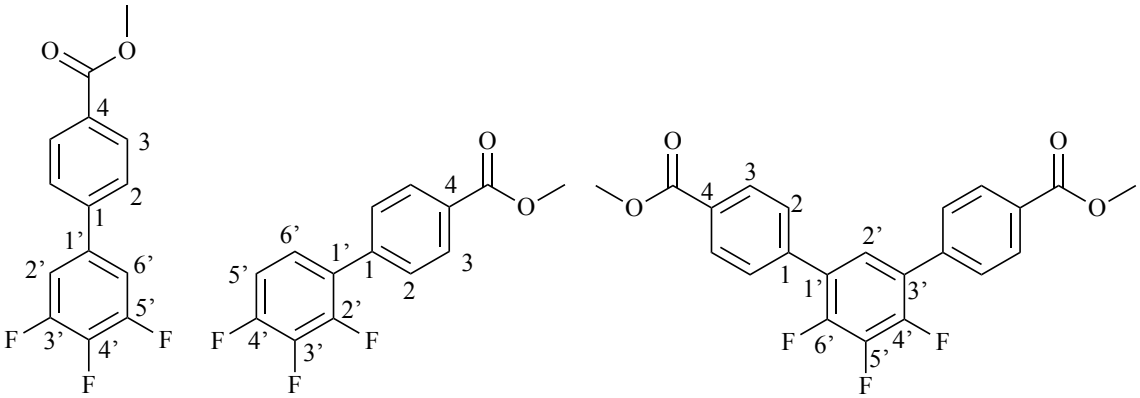
General procedure A [1, 2, 3, 4, 5-pentafluorobenzene (0.11 mL, 1.00 mmol, 1.0 equiv.),

B_2pin_2 (304.7 mg, 1.20 mmol, 1.2 equiv.), 100% conversion at 60 ℃ after 2 h] and B3 [$Pd_2(dba)_3$ (45.8 mg, 5 mol%), CsF (303.8 mg, 2.00 mmol, 2.0 equiv.), P(t-Bu)$_3$·HBF_4 (29.0 mg, 10 mol%), CuCl (198.0 mg, 2.00 mmol, 2.0 equiv.) and iodobenzene (0.11 mL, 1.00 mmol, 1.0 equiv.) at 100 ℃ for 13 h] were applied in a one-pot protocol. Flash column chromatography (0-5% chloroform in hexane) afforded the desired cross-coupled arene **70b** as a white solid (90.5 mg, 0.37 mmol, 37%). M.p. 101.3-101.7 ℃; ν_{max} (ATR) 1656, 1581, 1527, 1496, 1444, 1322, 1201, 1067, 983, 853, 798, 751, 723, 695, 652, 495 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 7.53 ~ 7.45 (3H, m, 3', 4'-*H*), 7.45 ~ 7.40 (2H, m, 2'-*H*); δ_C (176 MHz, $CDCl_3$) 144.3 (dm, *J* = 248 Hz, C-2), 140.5 (dm, *J* = 254 Hz, C-4), 138.0 (dm, *J* = 251 Hz, C-3), 130.3 (s, C-2'), 129.5 (s, C-4'), 128.9 (s, C-3'), 126.6 (s, C-1'), 116.1 (td, *J* = 17, 4 Hz, C-1); δ_F (376 MHz, $CDCl_3$) -143.3 (2F, dd, *J* = 21, 8 Hz, F-2), -155.6 (1F, t, *J* = 21 Hz, F-4), -162.3 (2F, td, *J* = 21, 8 Hz, F-3); HRMS (ASAP) m/z found $[M]^+$ 244.0314, $C_{12}H_5F_5$ requires *M*, 244.0311. Data for this compound were consistent with previous reports.[84]

71d: methyl 2',3',4'-trifluoro-[1,1'-biphenyl]-4-carboxylate

71e: methyl 3',4',5'-trifluoro-[1,1'-biphenyl]-4-carboxylate

71f: dimethyl 4',5',6'-trifluoro-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate



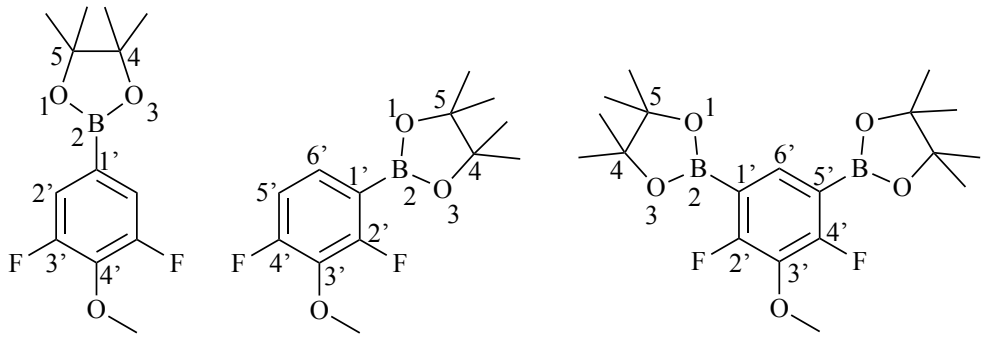
General procedure A [1, 2, 3-trifluorobenzene (0.10 mL, 1.00 mmol, 1.0 equiv.), B_2pin_2 (152.4 mg, 0.60 mmol, 0.6 equiv.), 86% conversion (**71a** : **71b** : **71c** = 1 : 2 : 1) at room temperature after 1 h] and B1 [$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (22.0 mg, 2.5 mol%), K_3PO_4 (343.9 mg, 1.62 mmol, 1.6 equiv.) and methyl 4-iodobenzoate (283.0 mg, 1.08 mmol, 1.1 equiv.) at 80 ℃ for 3 h] were applied in a one-pot protocol. Flash column chromatography (0-5% Et_2O in hexane) afforded a mixture of two mono cross-coupled arenes (**71d** and **71e**) as a white solid (124.5 mg, 0.47 mmol, 47%, ratio by ^{19}F NMR was 32 : 68). And then (15-20% Et_2O in hexane) afforded the bis cross-coupled arene **71f** as a white solid (74.6 mg, 0.19 mmol, 19%). **71d**: δ_H (700 MHz, $CDCl_3$) 8.13 ~ 8.09 (2H, m, 3-*H*), 7.58 ~ 7.54 (2H, m, 2-*H*), 7.25 ~ 7.19 (2H, m, 2'-*H*), 3.94 (3H, s, OCH_3); δ_C (176 MHz, $CDCl_3$) 166.7 (s, C=O), 151.1 (ddd, *J* = 252, 10, 3 Hz, C-3'), 142.5 (d, *J* = 2 Hz, C-1), 139.7 (dt, *J* = 253, 15 Hz, C-4'), 136.2 (td, *J* = 8, 5 Hz, C-1'), 130.2 (s, C-4), 130.0 (s, C-3), 127.0 (s, C-2), 111.5 (dd, *J* = 17, 4 Hz, C-2'), 52.4 (s,

OCH_3); δ_F (376 MHz, $CDCl_3$) -134.2 (2F, dd, *J* = 21, 8 Hz, F-3'), -161.1 (1F, t, *J* = 21 Hz, F-4'). **71e**: δ_H (700 MHz, $CDCl_3$) 8.13 ~ 8.09 (2H, m, 3-*H*), 7.58 ~ 7.54 (2H, m, 2-*H*), 7.17 (1H, dddd, *J* = 9, 8, 6, 2 Hz, 6'-*H*), 7.10 ~ 7.02 (1H, m, 5'-*H*), 3.94 (3H, s, OC*H*$_3$); δ_C (176 MHz, $CDCl_3$) 166.8 (s, C=O), 151.7 (ddd, *J* = 250, 10, 4 Hz, C-2'), 149.0 (ddd, *J* = 253, 11, 4 Hz, C-4'), 140.5 (dt, *J* = 252, 16 Hz, C-3'), 138.6 (s, C-1), 130.5 (s, C-4), 130.0 (s, C-3), 129.0 (d, *J* =3 Hz, C-2), 125.9 (dd, *J* = 11, 4 Hz, C-1'), 124.0 (dt, *J* = 8, 4 Hz C-6'), 112.5 (dd, *J* = 17, 4 Hz, C-5'), 52.4 (s, OCH_3); δ_F (376 MHz, $CDCl_3$) -133.5 (1F, d, *J* = 21 Hz, F-2'), -138.1 (1F, dd, *J* = 21, 8 Hz, F-4'), -159.5 (1F, t, *J* = 21 Hz, F-3'). **71f**: M.p. 173.4-173.9 °C; ν_{max} (ATR) 2992, 1727, 1474, 1402, 1119, 1029, 894, 733, 704 cm $^{-1}$; δ_H (700 MHz, $CDCl_3$) 8.14 (4H, d, *J* = 8.3 Hz, 3-*H*), 7.62 (4H, d, *J* = 8.3 Hz, 2-*H*), 7.30 (1H, td, *J* = 7.7, 2.2 Hz, 2'-*H*), 3.95 (6H, s, OC*H*$_3$); δ_C (176 MHz, $CDCl_3$) 166.7 (s, C=O), 148.5 (ddd, *J* = 254, 11, 3 Hz, C-4'), 140.9 (dm, *J* = 251.1 Hz, C-5'), 138.4 (s, C-1), 130.3 (s, C-4), 130.2 (s, C-3), 129.0 (s, C-2), 125.8 (dd, *J* = 10, 5 Hz, C-1'), 124.7 ~ 124.5 (m, C-2'), 52.4 (s, OCH_3); δ_F (376 MHz, $CDCl_3$) -137.8 (2F, d, *J* = 21 Hz, F-4'), -157.9 (1F, t, *J* = 21 Hz, F-5'); HRMS (ASAP) m/z found $[M+H]^+$ 401.1013, $C_{22}H_{16}F_3O_4$ requires *M*, 401.1001.

73a: 2-(3,5-difluoro-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

73b: 2-(2,4-difluoro-3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

73c: 2,2'-(4,6-difluoro-5-methoxy-1,3-phenylene)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)



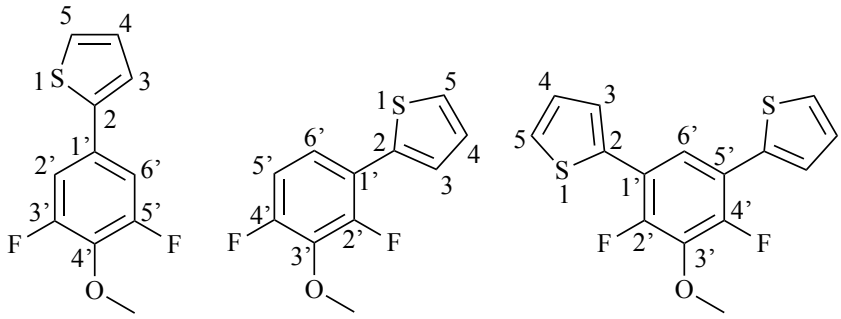
General procedure A was applied to 1,3-difluoro-2-methoxybenzene (0.24 mL, 2.00 mmol, 1.0 equiv.) and B_2pin_2 (304.7 mg, 1.20 mmol, 0.6 equiv.) at 60 ℃ with a reaction time of 4 h. Flash column chromatography (5-10% Et_2O in hexane) afforded a mixture of three borylated products (**73a**, **73b** and **73c**) as a colourless oil (382.5 mg, 1.34 mmol, 67%, ratio by ^{19}F NMR was 34 : 54 : 2). **73a**: δ_H (700 MHz, $CDCl_3$) 7.31 ~ 7.25 (2H, m, 2'-*H*), 4.00 (3H, s, OC*H*$_3$), 1.30 (12H, s, 4-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 155.2 (dd, *J* = 249, 5 Hz, C-3'), 139.03 (t, *J* = 14 Hz, C-4'), 123.6 (br s, C-1'), 118.1 (dd, *J* = 17, 4 Hz, C-2'), 84.3 (s, C-4), 61.6 (t, *J* = 4 Hz, OCH_3), 24.9 (s, $OCCH_3$); δ_F (376 MHz, $CDCl_3$) -129.9 (2F, s); δ_B (128 MHz, $CDCl_3$) 30.0. Data for this compound were consistent with previous reports.[85] **73b**: δ_H (700 MHz, $CDCl_3$) 7.34 (1H, dt, *J* = 8.4, 6.2 Hz, 6'-*H*), 6.85 (1H, ddd, *J* = 10.0, 8.4, 1.5 Hz, 5'-*H*), 3.94 (3H, s, OC*H*$_3$), 1.33 (12H, s, 4-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 160.6 (dd, *J* = 253, 5 Hz, C-2'), 158.4 (dd, *J* = 252, 6 Hz, C-4'), 136.4 (dd, *J* = 16, 13 Hz, C-3'), 130.1 (t, *J* = 10 Hz, C-6'), 113.2 (br s, C-

1'), 112.1 (dd, J = 19, 3 Hz, C-5'), 84.1 (s, C-4), 61.9 (t, J = 3 Hz, OCH_3), 24.8 (s, $OCCH_3$); δ_F (376 MHz, $CDCl_3$) -118.3 (1F, d, J = 13 Hz, F-4'), -124.0 (1F, d, J = 13 Hz, F-2'); δ_B (128 MHz, $CDCl_3$) 30.0. Data for this compound were consistent with previous reports.[82] **73c**: δ_H (700 MHz, $CDCl_3$) 7.77 (1H, t, J = 6.7 Hz, 6'-*H*), 3.96 (3H, s, OCH_3), 1.34 (24H, s, 4-CH_3); δ_C (176 MHz, $CDCl_3$) 162.9 (dd, J = 259, 7 Hz, C-2'), 137.6 (t, J = 10 Hz, C-6'), 136.2 (t, J = 15 Hz, C-3'), 84.1 (s, C-4), 62.0 (m, OCH_3), 24.9 (s, $OCCH_3$); δ_F (376 MHz, $CDCl_3$) -113.6 (2F, s); δ_B (128 MHz, $CDCl_3$) 29.9; HRMS (ESI) m/z found $[M+H]^+$ 395.2221, $C_{19}H_{29}{}^{10}B_2F_2O_5$ requires M, 395.2242.

73d: 2-(3,5-difluoro-4-methoxyphenyl)thiophene

73e: 2-(2,4-difluoro-3-methoxyphenyl)thiophene

73f: 2,2'-(4,6-difluoro-5-methoxy-1,3-phenylene)dithiophene

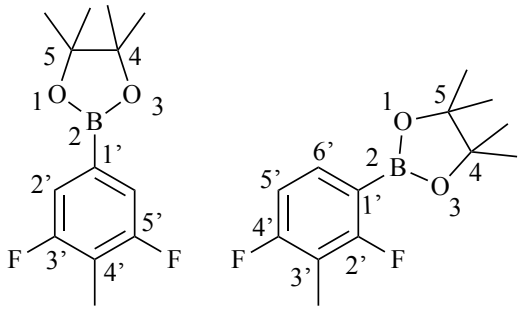


General procedure B4 was applied to a mixture (ratio by ^{19}F NMR was 15 : 35 : 50) of **73a** (10.3 mg, 0.04 mmol), **73b** (23.9 mg, 0.09 mmol) and **73c** (50.3 mg, 0.13 mmol), $Pd(dppf)Cl_2$ (27.9 mg, 10 mol%), TBAB (12.3 mg, 10 mol%), 2M aq. Na_2CO_3 (0.38 mL), 2-iodothiophene (0.06 mL, 0.57 mmol, 1.5 equiv.) and toluene (1.9 mL) at 110 °C with a reaction time of 23 h. Flash column chromatography (petroleum ether) afforded a mixture of two mono cross-coupled arenes (**73d** and **73e**) as a colourless oil

(24.4 mg, 0.11 mmol, 41%, ratio by ^{19}F NMR was 27 : 73) and the bis cross-coupled arene **73f** as yellow needle-like crystals (17.0 mg, 0.06 mmol, 22%). **73d**: δ_H (599 MHz, $CDCl_3$) 7.30 (1H, dd, *J* = 5.2, 1.2 Hz, 5-*H*), 7.28 ~ 7.21 (1H, m, 3-*H*), 7.17 ~ 7.09 (2H, m, 2'-*H*), 7.07 (1H, dd, *J* = 5.2, 3.6 Hz, 4-*H*), 4.02 (3H, s, OC*H*$_3$); δ_C (151 MHz, $CDCl_3$) 156.0 (dd, *J* = 248, 7 Hz, C-3'), 142.0 (s, C-2), 136.3 (dd, *J* = 3, 1 Hz, C-4'), 129.8 (s, C-1'), 128.3 (s, C-4), 125.7 (s, C-5), 124.0 (s, C-3), 109.8 (dd, *J* = 19, 6 Hz, C-2'), 62.1(s, OCH_3); δ_F (376 MHz, $CDCl_3$) -128.2 (2F, s). **73e**: δ_H (599 MHz, $CDCl_3$) 7.40 (1H, dd, *J* = 3.4, 1.6 Hz, 5-*H*), 7.36 (1H, dd, *J* = 5.1, 1.6 Hz, 3-*H*), 7.28 ~ 7.21 (1H, m, 6'-*H*), 7.17 ~ 7.09 (1H, m, 4-*H*), 6.92 (1H, ddd, *J* = 10.5, 8.9, 1.9 Hz, 5'-H), 4.04 (3H, s, OC*H*$_3$); δ_C (151 MHz, $CDCl_3$) 155.1 (dd, *J* = 252, 8 Hz, C-4'), 152.8 (dd, *J* = 252, 6 Hz, C-2'), 137.3 (t, *J* = 14 Hz, C-3'), 135.8 (s, C-2), 127.8 (s, C-4), 126.4 (dd, *J* = 6, 1 Hz, C-5), 125.9 (d, *J* = 4 Hz, C-3), 122.0 (dd, *J* = 9, 4 Hz, C-6'), 119.8 (dd, *J* = 12, 4 Hz, C-1'), 112.3 (dd, *J* = 20, 4 Hz, C-5'), 62.2 (s, OCH_3); δ_F (376 MHz, $CDCl_3$) -129.3 (1F, d, *J* = 9.2 Hz, F-4'), -129.4 (1F, d, *J* = 9.2 Hz, F-2'). **73f**: M.p. 48.7-49.3 °C; ν_{max} (ATR) 2950, 2844, 1536, 1467, 1430, 1114, 998, 982, 832, 736, 698 cm $^{-1}$; δ_H (599 MHz, $CDCl_3$) 7.52 (1H, t, *J* = 7.7 Hz, 6'-*H*), 7.44 (2H, dd, *J* = 3.6, 1.1 Hz, 5-*H*), 7.40 (2H, dd, *J* = 5.2, 1.1 Hz, 3-*H*), 7.14 (2H, dd, *J* = 5.2, 3.6 Hz, 4-*H*), 4.08 (3H, s, OC*H*$_3$); δ_C (151 MHz, $CDCl_3$) 151.8 (dd, *J* = 254, 5 Hz, C-2'), 137.8 (t, *J* = 15 Hz, C-3'), 135.9 (t, *J* = 2 Hz, C-2), 127.9 (s, C-4), 126.7 (t, *J* = 4 Hz, C-5), 126.2 (s, C-3), 121.3 (t, *J* = 4 Hz, C-6'), 119.7 (dd, *J* = 11, 6 Hz, C-1'), 62.4 (s, OCH_3); δ_F (376 MHz, $CDCl_3$) -130.1 (2F, s); HRMS (ASAP) m/z found $[M]^+$ 308.0149, $C_{15}H_{10}F_2OS_2$ requires *M*, 308.0141.

74a: 2-(3,5-difluoro-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

74b: 2-(2,4-difluoro-3-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

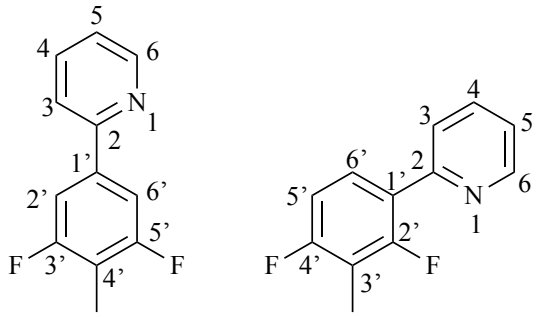


General procedure A was applied to 1,3-difluoro-2-methylbenzene (0.11 mL, 1.00 mmol, 1.0 equiv.) and B_2pin_2 (152.4 mg, 0.60 mmol, 0.6 equiv.) at 60 ℃ with a reaction time of 2 h. Flash column chromatography (15-25% EtOAc in hexane) afforded the borylated product **74a** as a colourless solid (53.4 mg, 0.21 mmol, 21%). A mixture of two mono borylated products (**74a** and **74b**) was eluted afterward as a colourless oil (101.4 mg, 0.40 mmol, 40%, ratio by ^{19}F NMR was 50 : 50). **74a**: ν_{max} (ATR) 2971, 1566, 1407, 1329, 1264, 1143, 1080, 964, 852, 736, 704, 690 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 7.24 (2H, dd, *J* = 6.3, 1.5 Hz, 2'-*H*), 2.21 (3H, s, 4'-C*H*$_3$), 1.33 (12H, s, 4-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 161.5 (dd, *J* = 247, 8 Hz, C-3'), 128.5 (br s, C-1'), 116.6 (t, *J* = 21 Hz, C-4'), 116.4 (dd, *J* = 19, 5 Hz, C-2'), 84.4 (s, C-4), 25.0 (s, $OCCH_3$), 7.4 (t, *J* = 4 Hz, 4'-CH_3); δ_F (376 MHz, $CDCl_3$) -115.9 (2F, s); δ_B (128 MHz, $CDCl_3$) 30.2; HRMS (ASAP) m/z found $[M+H]^+$ 254.1395, $C_{13}H_{18}{}^{10}BF_2O_2$ requires *M*, 254.1404. Data for this compound were consistent with previous reports.[69] **74b**: δ_H (700 MHz, $CDCl_3$) 7.53 (1H, q, *J* = 7.3 Hz, 6'-*H*), 6.80 (1H, t, *J* = 8.5 Hz, 5'-*H*), 2.16 (3H, s, 3'-C*H*$_3$), 1.34 (12H, s, 4-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 166.4 (dd, *J* = 252, 9 Hz, C-2'), 164.2 (dd, *J* = 250, 9 Hz, C-4'), 134.4 (t, *J* = 11 Hz, C-6'), 113.0 (ddd, *J* = 23, 21,

1 Hz, C-3'), 111.4 (br s, C-1'), 110.7 (dd, J = 22, 3 Hz, C-5'), 84.0 (s, C-4), 24.9 (s, $OCCH_3$), 6.9 (td, J = 4, 2 Hz, 3'-CH_3); δ_F (376 MHz, $CDCl_3$) -103.4 (1F, d, J = 12 Hz, F-4'), -109.8 (1F, d, J = 12 Hz, F-2'); δ_B (128 MHz, $CDCl_3$) 30.2.

74d: 2-(3,5-difluoro-4-methylphenyl)pyridine

74e: 2-(2,4-difluoro-3-methylphenyl)pyridine

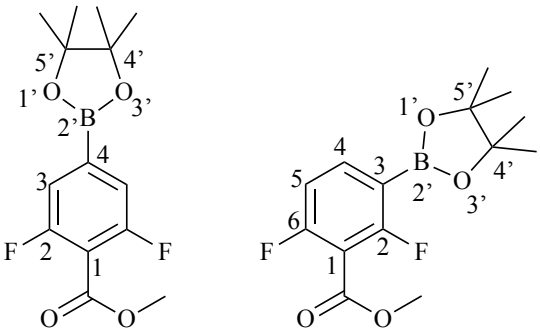


General procedure B4 was applied to a mixture (ratio by ^{19}F NMR was 68 : 32) of **74a** (168.2 mg, 0.66 mmol) and **74b** (79.1 mg, 0.31 mmol), Pd(dppf)Cl_2 (71.2 mg, 10 mol%), TBAB (31.4 mg, 10 mol%), 2M aq. Na_2CO_3 (0.97 mL), 2-iodopyridine (0.16 mL, 1.46 mmol, 1.5 equiv.) and toluene (4.9 mL) at 110 ℃ with a reaction time of 19 h. Flash column chromatography (0-5% chloroform in toluene) afforded the desired cross-coupled arenes **74d** (20.9 mg, 0.10 mmol, 11%) and **74e** (18.7 mg, 0.09 mmol, 9%) both as a light yellow oil. **74d**: ν_{max} (ATR) 2939, 1587, 1569, 1442, 1412, 1336, 1083, 735, 789, 704, 670 cm $^{-1}$; δ_H (599 MHz, $CDCl_3$) 8.68 (1H, d, J = 4.9 Hz, 6-H), 7.76 (1H, td, J = 7.8, 1.8 Hz, 4-H), 7.66 (1H, d, J = 7.8 Hz, 3-H), 7.55 ~ 7.48 (2H, m, 2'-H), 7.28 ~ 7.23 (1H, m, 5-H), 2.24 (3H, s, 4-CH_3); δ_C (151 MHz, $CDCl_3$) 162.1 (dd, J = 246, 10 Hz, C-3'), 155.2 (t, J = 3 Hz, C-2), 149.9 (s, C-6), 139.0 (t, J = 10 Hz, C-1'), 137.1 (s, C-4), 123.0 (s, C-5), 120.3 (s, C-3), 114.1 (s, C-4'), 109.4 ~ 109.0 (m, C-

2'), 7.3 (t, J = 4 Hz, 4'-CH_3); δ_F (376 MHz, $CDCl_3$) -114.5 (2F, s); HRMS (ASAP) m/z found $[M+H]^+$ 206.0760, $C_{12}H_{10}F_2N$ requires M, 206.0781. **74e**: ν_{max} (ATR) 2987, 1602, 1473, 1441, 1071, 786, 733, 679 cm $^{-1}$; δ_H (599 MHz, $CDCl_3$) 8.71 (1H, d, J = 4.8 Hz, 6-*H*), 7.80 ~ 7.70 (3H, m, 3, 4, 6'-*H*), 7.27 ~ 7.23 (1H, m, 5-*H*), 6.97 (1H, td, J = 8.6, 1.5 Hz, 5'-*H*), 2.27 (3H, s, 3'-C*H*$_3$); δ_C (151 MHz, $CDCl_3$) 161.8 (dd, J = 248, 9 Hz, C-4'), 159.1 (dd, J = 250, 9 Hz, C-2'), 153.1 (s, C-1'), 149.6 (s, C-6), 136.5 (s, C-4), 128.4 (dd, J = 10, 5 Hz, C-6'), 124.2 (d, J = 9 Hz, C-3), 123.3 (dd, J = 13, 4 Hz, C-2), 122.3 (s, C-5), 114.1 ~ 112.8 (m, C-3'), 111.1 (dd, J = 23, 4 Hz, C-5'), 7.3 ~ 7.2 (m, 3'-CH_3); δ_F (376 MHz, $CDCl_3$) -113.5 (1F, d, J = 10 Hz, F-4'), -117.8 (1F, d, J = 10 Hz, F-2'); HRMS (ASAP) m/z found $[M+H]^+$ 206.0781, $C_{12}H_{10}F_2N$ requires M, 206.0781.

75a: methyl 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

75b: methyl 2,6-difluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate

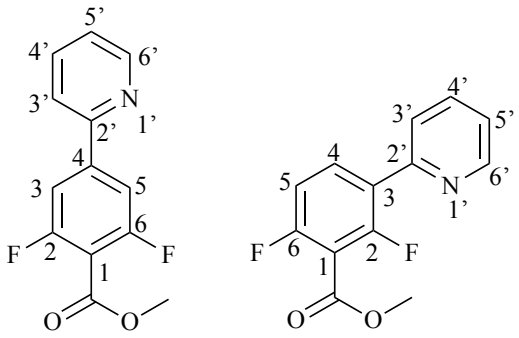


General procedure A was applied to methyl 2,6-difluorobenzoate (0.27 mL, 2.00 mmol, 1.0 equiv.) and B_2pin_2 (304.7 mg, 1.20 mmol, 0.6 equiv.) at room temperature with a reaction time of 19 h. Flash column chromatography (0-15% EtOAc in hexane) afforded the borylated product **75a** as a colourless solid (265.2 mg, 0.89 mmol, 45%).

A mixture of two mono borylated products (**75a** and **75b**) was eluted afterward as a colourless oil (172.6 mg, 0.58 mmol, 30%, ratio by ^{19}F NMR was 52 : 48). **75a**: M.p. 58.6-59.8 °C; ν_{max} (ATR) 2993, 1741, 1425, 1371, 1146, 1033, 963, 904, 851, 733, 706 cm $^{-1}$; δ_H (700 MHz, $CDCl_3$) 7.33 (2H, s, 3-*H*), 3.93 (3H, s, OC*H*$_3$), 1.33 (12H, s, 4'-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 162.2 (s, C=O), 160.2 (dd, *J* = 258, 5 Hz, C-2), 135.2 (br s, C-4), 117.5 (dd, *J* = 20, 4 Hz, C-3), 113.1 (t, *J* = 18 Hz, C-1), 84.9 (s, C-4'), 52.9 (s, OCH_3), 24.9 (s, $OCCH_3$); δ_F (376 MHz, $CDCl_3$) -111.6 (2F, s); δ_B (128 MHz, $CDCl_3$) 29.9; HRMS (ASAP) m/z found $[M+H]^+$ 298.1317, $C_{14}H_{18}{}^{10}BF_2O_4$ requires *M*, 298.1303. Data for this compound were consistent with previous reports.[86] **75b**: δ_H (700 MHz, $CDCl_3$) 7.76 ~ 7.70 (1H, m, 4-*H*), 6.86 (1H, t, *J* = 8.7 Hz, 5-*H*), 3.85 (3H, s, OC*H*$_3$), 1.26 (12H, s, 4'-C*H*$_3$); δ_C (176 MHz, $CDCl_3$) 165.0 (dd, *J* = 261, 6 Hz, C-2), 162.9 (dd, *J* = 261, 6 Hz, C-6), 162.2 (s, C=O), 140.0 (t, *J* = 11 Hz, C-4), 111.8 (dd, *J* = 21, 4 Hz, C-5), 110.99 (dd, *J* = 21, 18 Hz, C-1), 84.3 (s, C-4'), 52.8 ~ 52.7 (m, OCH_3), 24.9 (s, $OCCH_3$); δ_F (376 MHz, $CDCl_3$) -99.3 (1F, dd, *J* = 7, 3 Hz, F-2), -106.2 (1F, d, *J* = 7 Hz, F-6); δ_B (128 MHz, $CDCl_3$) 29.8.

75d: methyl 2,6-difluoro-4-(pyridin-2-yl)benzoate

75e: methyl 2,6-difluoro-3-(pyridin-2-yl)benzoate

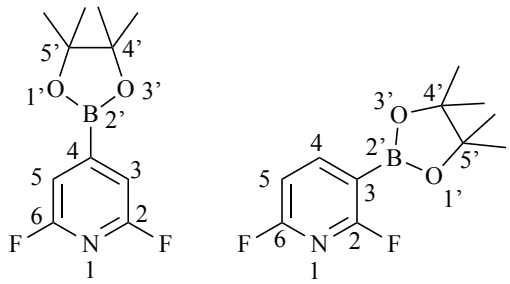


General procedure B4 was applied to a mixture (ratio by ^{19}F NMR was 52 : 48) of **75a** (86.3 mg, 0.29 mmol) and **75b** (79.7 mg, 0.27 mmol), Pd(dppf)Cl_2 (40.7 mg, 10 mol%), TBAB (18.0 mg, 10 mol%), 2M aq. Na_2CO_3 (0.56 mL), 2-iodopyridine (0.09 mL, 0.84 mmol, 1.5 equiv.) and toluene (2.8 mL) at 110 ℃ with a reaction time of 3 h. Flash column chromatography (90-100% DCM in hexane) afforded the desired cross-coupled arene **75d** as a white solid (33.6 mg, 0.14 mmol, 25%) and **75e** as a light yellow solid (48.6 mg, 0.20 mmol, 36%). **75d**: M.p. 78.2-78.6 ℃; ν_{max} (ATR) 3078, 2960, 1736, 1631, 1565, 1415, 1347, 1114, 1040, 779, 738, 537 cm $^{-1}$; δ_H (599 MHz, $CDCl_3$) 8.71 (1H, ddd, *J* = 4.8, 1.8, 0.9 Hz, 6'-*H*), 7.81 (1H, td, *J* = 7.8, 1.8 Hz, 4'-*H*), 7.72 (1H, dt, *J* = 7.8, 1.1 Hz, 3'-*H*), 7.64 (2H, d, *J* = 9.2 Hz, 3-*H*), 7.33 (1H, ddd, *J* = 7.8, 4.8, 1.1 Hz, 5'-*H*), 3.97 (3H, s, OCH_3); δ_C (151 MHz, $CDCl_3$) 162.1 (s, C=O), 161.3 (dd, *J* = 256, 9 Hz, C-2), 153.7 (t, *J* = 3 Hz, C-2'), 150.1 (s, C-6'), 144.5 (t, *J* = 10 Hz, C-4), 137.4 (s, C-4'), 124.0 (s, C-5'), 120.9 (s, C-3'), 110.7 (t, *J* = 18 Hz, C-1), 110.4 (dd, *J* = 23, 5 Hz, C-3), 52.93 (s, OCH_3); δ_F (376 MHz, $CDCl_3$) -109.4 (2F, s); HRMS (ASAP) m/z found $[M+H]^+$ 250.0674, $C_{13}H_{10}F_2NO_2$ requires *M*, 250.0680. **75e**: M.p. 90.8-91.4

°C; ν_{max} (ATR) 3035, 2965, 1737, 1624, 1598, 1441, 1327, 1143, 1089, 996, 795, 746, 571 cm $^{-1}$; δ_H (599 MHz, $CDCl_3$) 8.71 (1H, dt, *J* = 4.8, 1.4 Hz, 6'-*H*), 8.12 (1H, td, *J* = 8.8, 6.4 Hz, 4-*H*), 7.78 ~7.74 (2H, m, 3', 4'-*H*), 7.28 (1H, td, *J* = 4.8, 3.9 Hz, 5'-*H*), 7.08 (1H, td, *J* = 8.8, 1.3 Hz, 5-*H*), 3.97 (3H, s, OC*H*$_3$); δ_C (151 MHz, $CDCl_3$) 162.2 (s, C=O), 160.7 (dd, *J* = 258, 6 Hz, C-6), 158.2 (dd, *J* = 260, 6 Hz, C-2), 151.8 (d, *J* = 2 Hz, C-3), 150.0 (s, C-6'), 136.8 (s, C-4'), 134.3 (dd, *J* = 10, 5 Hz, C-4), 124.5 (d, *J* = 10 Hz, C-2'), 124.4 (s, C-3'), 123.0 (s, C-5'), 112.6 (dd, *J* = 22, 4 Hz, C-5), 111.5 (dd, *J* = 20, 19 Hz, C-1), 53.0 (s, OCH_3); δ_F (376 MHz, $CDCl_3$) -109.6 (1F, d, *J* = 4 Hz, F-6), -114.5 (1F, d, *J* = 4 Hz, F-2); HRMS (ASAP) m/z found $[M]^+$ 249.0598, $C_{13}H_9F_2NO_2$ requires *M*, 249.0601.

76a: 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

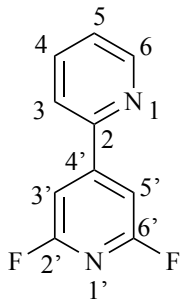
76b: 2,6-difluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



General procedure A was applied to 6-fluoropyridin-2-amine (0.09 mL, 1.00 mmol, 1.0 equiv.) and B_2pin_2 (152.4 mg, 0.60 mmol, 1.2 equiv.) at room temperature with a reaction time of 3 h. Flash column chromatography (0-10% EtOAc in hexane) afforded the borylated product **76a** as colourless needlelike crystals (137.1 mg, 0.57 mmol, 57%). A mixture of two mono borylated products (**76a** and **76b**) was eluted afterward as a

white solid (47.7 mg, 0.20 mmol, 20%, ratio by ^{19}F NMR was 55 : 45). **76a**: M.p. 57.2-57.8 °C; ν_{max} (ATR) 3057, 2993, 1605, 1405, 1387, 1190, 1145,1022, 734, 705 cm $^{-1}$; δ_H (599 MHz, $CDCl_3$) 7.13 (2H, s, 3-*H*), 1.33 (12H, s, 4'-C*H*$_3$); δ_C (151 MHz, $CDCl_3$) 161.6 (dd, *J* = 249, 14 Hz, C-2), 148.5 (s, C-4), 111.1 ~ 111.0 (m, C-3), 85.3 (s, C-4'), 24.9 (s, $OCCH_3$); δ_F (376 MHz, $CDCl_3$) -69.4 (2F, s); δ_B (128 MHz, $CDCl_3$) 29.5; HRMS (ASAP) m/z found $[M+H]^+$ 241.1209, $C_{11}H_{15}{}^{10}BF_2NO_2$ requires *M*, 241.1200. Data for this compound were consistent with previous reports.[68] **76b**: δ_H (599 MHz, $CDCl_3$) 8.24 (1H, q, *J* = 8.2 Hz, 4-*H*), 6.80 (1H, ddd, *J* = 7.9, 2.6, 1.3 Hz, 5-*H*), 1.34 (12H, s, 4'-C*H*$_3$); δ_C (151 MHz, $CDCl_3$) 165.7 (dd, *J* = 264, 15 Hz, C-2), 164.0 (dd, *J* = 262, 15 Hz, C-6), 152.6 (t, *J* = 7.7 Hz, C-4), 105.9 (dd, *J* = 33, 6 Hz, C-5), 84.7 (s, C-4'), 24.9 (s, $OCCH_3$); δ_F (376 MHz, $CDCl_3$) -57.2 (1F, d, *J* = 10 Hz, F-2), -63.8 (1F, d, *J* = 10 Hz, F-6); δ_B (128 MHz, $CDCl_3$) 29.5. Data for this compound were consistent with previous reports.[68]

76d: 2',6'-difluoro-2,4'-bipyridine

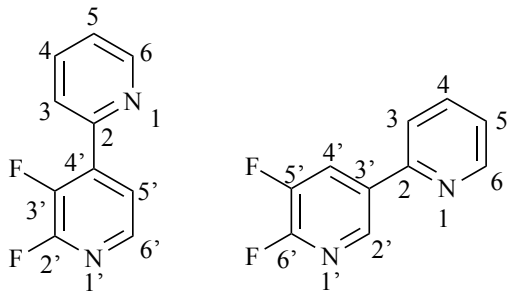


General procedure B4 was applied to **76a** (166.1 mg, 0.69 mmol), Pd(dppf)Cl_2 (50.4 mg, 10 mol%), TBAB (22.2 mg, 10 mol%), 2M aq. Na_2CO_3 (0.69 mL), 2-iodopyridine (0.11 mL, 1.03 mmol, 1.5 equiv.) and toluene (3.5 mL) at 110 °C with a reaction time

of 45 h. Flash column chromatography (5-15% EtOAc in hexane) afforded the desired cross-coupled arene **76d** as a light yellow solid (54.6 mg, 0.29 mmol, 41%). M.p. 83.2-84.6 °C; ν_{max} (ATR) 3121, 2939, 2858, 1635, 1566, 1406, 1366, 1160, 1031, 883, 785, 679 cm^{-1}; δ_H (599 MHz, $CDCl_3$) 8.76 (1H, ddd, *J* = 4.8, 1.9, 1.0 Hz, 6-*H*), 7.89 ~ 7.83 (1H, m, 4-*H*), 7.79 (1H, dd, *J* = 8.0, 1.0 Hz, 3-*H*), 7.46 (2H, d, *J* = 0.8 Hz, 3'-*H*), 7.41 (1H, ddt, *J* = 6.7, 4.8, 1.0 Hz, 5-*H*); δ_C (151 MHz, $CDCl_3$) 162.6 (dd, *J* = 246, 16 Hz, C-2'), 156.5 (t, *J* = 8 Hz, C-4'), 152.5 (t, *J* = 4 Hz, C-2), 150.4 (s, C-6), 137.5 (s, C-4), 125.1(s, C-5), 121.3(s, C-3), 103.9 ~ 103.5 (m, C-3'); δ_F (376 MHz, $CDCl_3$) -68.1 (2F, s); HRMS (ESI) m/z found $[M+H]^+$ 193.0581, $C_{10}H_7F_2N_2$ requires *M*, 193.0577.

80d: 2',3'-difluoro-2,4'-bipyridine

80e: 5',6'-difluoro-2,3'-bipyridine

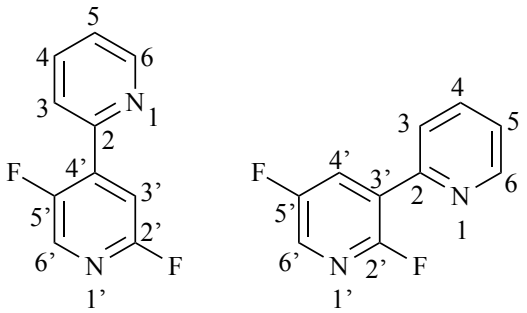


General procedure A [2,3-difluoropyridine (0.09 mL, 1.00 mmol, 1.0 equiv.), B_2pin_2 (152.4 mg, 0.60 mmol, 0.6 equiv.), 91% conversion (**80a** : **80b** : **80c** = 6 : 1 : 0.5) at room temperature after 11 h] and B4 [Pd(dppf)Cl_2 (66.6 mg, 10 mol%), TBAB (29.3 mg, 10 mol%), 2M aq. Na_2CO_3 (0.91 mL), 2-iodopyridine (0.15 mL, 1.37 mmol, 1.5 equiv.) and toluene (4.6 mL) at 110 °C for 15 h] were applied in a one-pot protocol. Flash column chromatography (2-4% Et_2O in DCM) afforded the desired cross-coupled

arenes **80d** (22.5 mg, 0.12 mmol, 12%) and **80e** (13.1 mg, 0.07 mmol, 7%) both as a white solid. **80d**: M.p. 42.3-43.5 °C; ν_{max} (ATR) 2934, 2854, 1624, 1591, 1481, 1466, 1451, 1430,1269, 1208, 1087, 918, 789, 734, 705 cm^{-1}; δ_H (599 MHz, $CDCl_3$) 8.78 (1H, dd, *J* = 4.7, 1.6 Hz, 6-*H*), 8.05 (1H, dd, *J* = 5.0, 1.3 Hz, 6'-*H*), 7.91 (1H, d, *J* = 7.9 Hz, 3-*H*), 7.88 (1H, td, *J* = 5.0, 1.0 Hz, 5'-*H*), 7.85 (1H, tt, *J* = 7.9, 1.4 Hz, 4-*H*), 7.42 ~ 7.36 (1H, m, 5-*H*); δ_C (151 MHz, $CDCl_3$) 153.2 (dd, *J* = 238, 16 Hz, C-2'), 150.4 (s, C-6), 145.0 (dd, *J* = 4, 3 Hz, C-2), 143.7 (dd, *J* = 264, 29 Hz, C-3'), 141.4 (dd, *J* = 14, 8 Hz, C-6'), 138.0 (dd, *J* = 7, 3 Hz, C-4'), 137.1 (s, C-4), 125.3 (d, *J* = 10 Hz, C-3), 124.5 (s, C-5), 122.5 (d, *J* = 4 Hz, C-5'); δ_F (376 MHz, $CDCl_3$) -88.3 (1F, d, *J* = 27 Hz, F-2'), -146.0 (1F, d, *J* = 27 Hz, F-3'); HRMS (ASAP) m/z found $[M+H]^+$ 193.0581, $C_{10}H_7F_2N_2$ requires *M*, 193.0577. **80e**: M.p. 80.2-82.2 °C; ν_{max} (ATR) 2934, 2859, 1592, 1494, 1468, 1446, 1411, 1171, 996, 786, 734, 709 cm^{-1}; δ_H (599 MHz, $CDCl_3$) 8.76 ~ 8.67 (1H, m, 6-*H*), 8.54 (1H, s, 2'-*H*), 8.32 ~ 8.26 (1H, m, 4'-*H*), 7.81 (1H, td, *J* = 7.6, 1.6 Hz, 4-*H*), 7.77 ~ 7.70 (1H, m, 3-*H*), 7.32 (1H, ddd, *J* = 7.6, 4.8, 1.1 Hz, 5-*H*); δ_C (151 MHz, $CDCl_3$) 152.6 (d, *J* = 1Hz, C-2), 152.4 (dd, *J* = 242, 15 Hz, C-6'), 150.3 (s, C-6), 145.8 (dd, *J* = 261, 28 Hz, C-5'), 139.7 (dd, *J* = 13, 6 Hz, C-2'), 137.4 (s, C-4), 135.2 (dd, *J* = 5, 1 Hz, C-3'), 125.4 (dd, *J* = 16, 4 Hz, C-4'), 123.5 (s, C-5), 120.6 (s, C-3); δ_F (376 MHz, $CDCl_3$) -87.4 (1F, d, *J* = 27 Hz, F-6'), -139.8 (1F, d, *J* = 27 Hz, F-5'); HRMS (ASAP) m/z found $[M+H]^+$ 193.0583, $C_{10}H_7F_2N_2$ requires *M*, 193.0577.

81e: 2',5'-difluoro-2,4'-bipyridine

81f: 2',5'-difluoro-2,3'-bipyridine

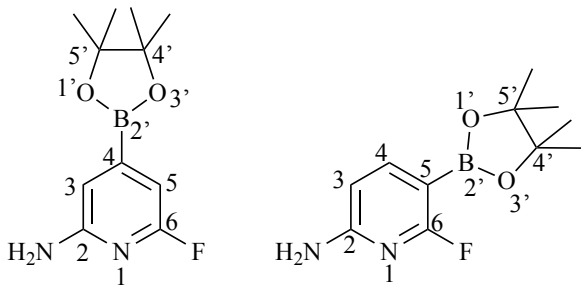


General procedure A [2,3-difluoropyridine (0.28 mL, 2.00 mmol, 1.0 equiv.), B_2pin_2 (304.7 mg, 1.20 mmol, 0.6 equiv.), 90% conversion (**81a** : **81b** : **81c** : **81d** = 1.6 : 1 : 0.1 : 0.1) at room temperature after 17 h] and B4 [Pd(dppf)Cl_2 (130.2 mg, 10 mol%), TBAB (57.4 mg, 10 mol%), 2M aq. Na_2CO_3 (1.8 mL), 2-iodopyridine (0.28 mL, 2.67 mmol, 1.5 equiv.) and toluene (8.9 mL) at 110 ℃ for 21 h] were applied in a one-pot protocol. Flash column chromatography (2-3% MeCN in chloroform) afforded a mixture of two mono cross-coupled arenes (**81e** and **81f**) as a white solid (135.1 mg, 0.70 mmol, 36%, ratio by ^{19}F NMR was 75 : 25). **81e**: δ_H (700 MHz, $CDCl_3$) 8.69 (1H, ddd, *J* = 4.8, 1.8, 1.0 Hz, 6-*H*), 8.32 (1H, ddd, *J* = 8.2, 7.4, 3.1 Hz, 6'-*H*), 8.02 (1H, dd, *J* = 3.1, 2.0 Hz, 3'-*H*), 7.90 (1H, ddt, *J* = 7.8, 1.8, 1.0 Hz, 3-*H*), 7.77 (1H, td, *J* = 7.8, 1.8 Hz, 4-*H*), 7.29 (1H, ddd, *J* = 7.8, 4.8, 1.8 Hz, 5-*H*); δ_C (176 MHz, $CDCl_3$) 157.9 (dd, *J* = 252, 4 Hz, C-2'), 156.2 (dd, *J* = 238, 1 Hz, C-5'), 150.2 (s, C-6), 149.9 (dd, *J* = 7, 1 Hz, C-2), 136.9 ~ 136.8 (m, C-4), 134.3 (dd, *J* = 28, 17 Hz, C-3'), 128.0 (dd, *J* = 23, 5 Hz, C-6'), 124.0 (d, *J* = 12 Hz, C-3), 123.6 (s, C-5), 123.2 (dd, *J* = 30, 5 Hz, C-4'); δ_F (376 MHz, $CDCl_3$) -73.8 (1F, d, *J* = 29 Hz, F-2'), -131.8 (1F, d, *J* = 29 Hz, F-5'). **81f**: δ_H (700 MHz, $CDCl_3$) 8.73 (1H, ddd, *J* = 4.8, 1.8, 1.0 Hz, 6-*H*), 8.11 (1H, dd,

J = 2.5, 1.9 Hz, 6'-*H*), 7.89 ~ 7.87 (1H, m, 3-*H*), 7.81 ~ 7.78 (1H, m, 4-*H*), 7.65 (1H, dd, *J* = 5.0, 1.9 Hz, 4'-*H*), 7.35 (1H, ddd, *J* = 7.6, 4.8, 1.1 Hz, 5-*H*); δ_C (176 MHz, $CDCl_3$) 160.1 (dd, *J* = 236, 2 Hz, C-2'), 155.12 (dd, *J* = 253, 5 Hz, C-5'), 150.0 (s, C-6), 149.5 (t, *J* = 3 Hz, C-2), 139.3 (dd, *J* = 12, 9 Hz, C-3'), 136.9 ~ 136.8 (m, C-4), 135.7 (dd, *J* = 31, 16 Hz, C-6'), 124.7 (d, *J* = 11 Hz, C-3), 124.5 (s, C-5), 109.60 (dd, *J* = 43, 1 Hz, C-4'); δ_F (376 MHz, $CDCl_3$) -72.7 (1F, d, *J* = 27 Hz, F-2'), -137.3 (1F, d, *J* = 27 Hz, F-5').

82a: 6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine

82b: 6-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine



General procedure A was applied to 6-fluoropyridin-2-amine (112.1 mg, 1.00 mmol, 1.0 equiv.) and B_2pin_2 (380.9 mg, 1.50 mmol, 1.5 equiv.) at room temperature with a reaction time of 23 h. Flash column chromatography (95-100% DCM in hexane) afforded the borylated product **82a** as a yellow solid (87.2 mg, 0.37 mmol, 37%). A mixture of two mono borylated products (**82a** and **82b**) was eluted afterward as a light yellow oily solid (30.6 mg, 0.13 mmol, 13%, ratio by ^{19}F NMR was 54 : 46). **82a**: ν_{max} (ATR) 3057, 1626, 1387, 1134, 909, 851, 730, 705 cm $^{-1}$; δ_H (599 MHz, $CDCl_3$) 6.68 (1H, d, *J* = 2.6 Hz, 3-*H*), 6.53 (1H, d, *J* = 2.1 Hz, 5-*H*), 4.36 (2H, s, NH_2), 1.32 (12H,

s, 4'-C*H*$_3$); δ_C (151 MHz, $CDCl_3$) 163.2 (d, *J* = 239 Hz, C-6), 157.5 (d, *J* = 16 Hz, C-2), 144.2 (br s, C-4), 110.3 (d, *J* = 4 Hz, C-3), 101.6 (d, *J* = 34 Hz, C-5), 84.7 (s, C-4'), 24.9 (s, $OCCH_3$); δ_F (376 MHz, $CDCl_3$) -72.1 (1F, s); δ_B (128 MHz, $CDCl_3$) 30.0; HRMS (ASAP) m/z found $[M]^+$ 237.1322, $C_{11}H_{16}{}^{10}BFN_2O_2$ requires *M*, 237.1325. **82b**: δ_H (599 MHz, $CDCl_3$) 7.86 (1H, t, *J* = 8.3 Hz, 4-*H*), 6.29 (1H, dd, *J* = 7.9, 2.6 Hz, 3-*H*), 4.35 (2H, br s, N*H*$_2$), 1.32 (12H, s, 4'-C*H*$_3$); δ_C (151 MHz, $CDCl_3$) 167.5 (d, *J* = 244 Hz, C-6), 160.1 (d, *J* = 18 Hz, C-2), 149.3 (d, *J* = 8 Hz, C-4), 104.4 (d, *J* = 4 Hz, C-3), 83.8 (s, C-4'), 24.9 (s, $OCCH_3$); δ_F (376 MHz, $CDCl_3$) -59.4 (1F, s); δ_B (128 MHz, $CDCl_3$) 30.0. Data for this compound were consistent with previous reports.[87]

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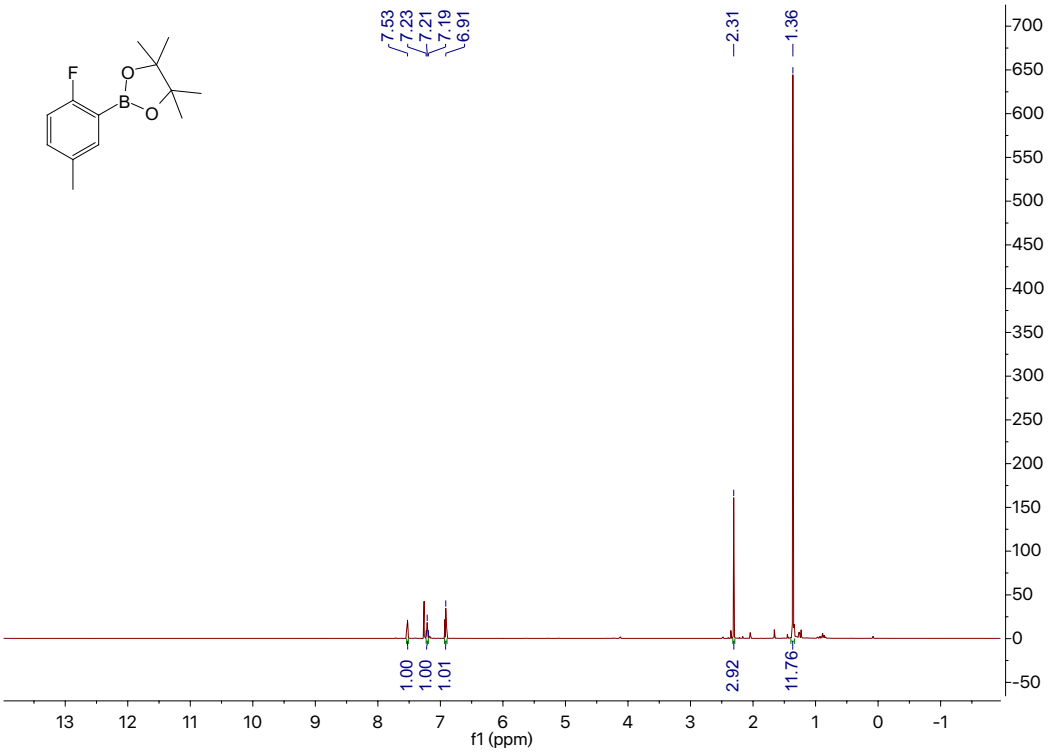
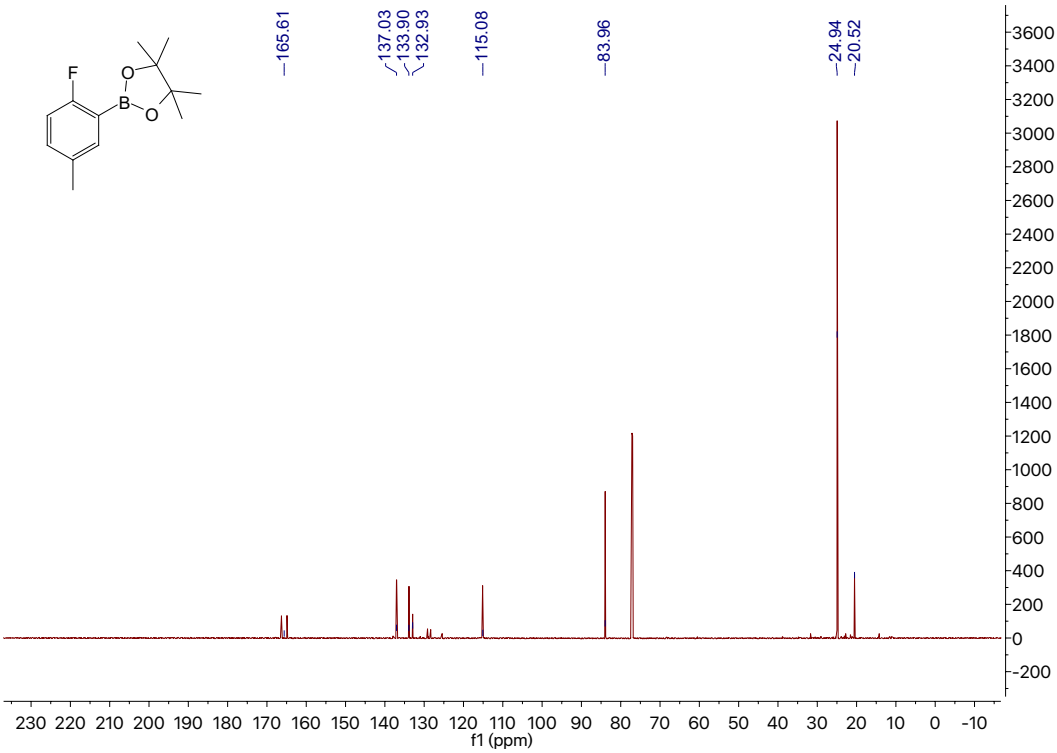
6.0 Appendix — NMR spectra

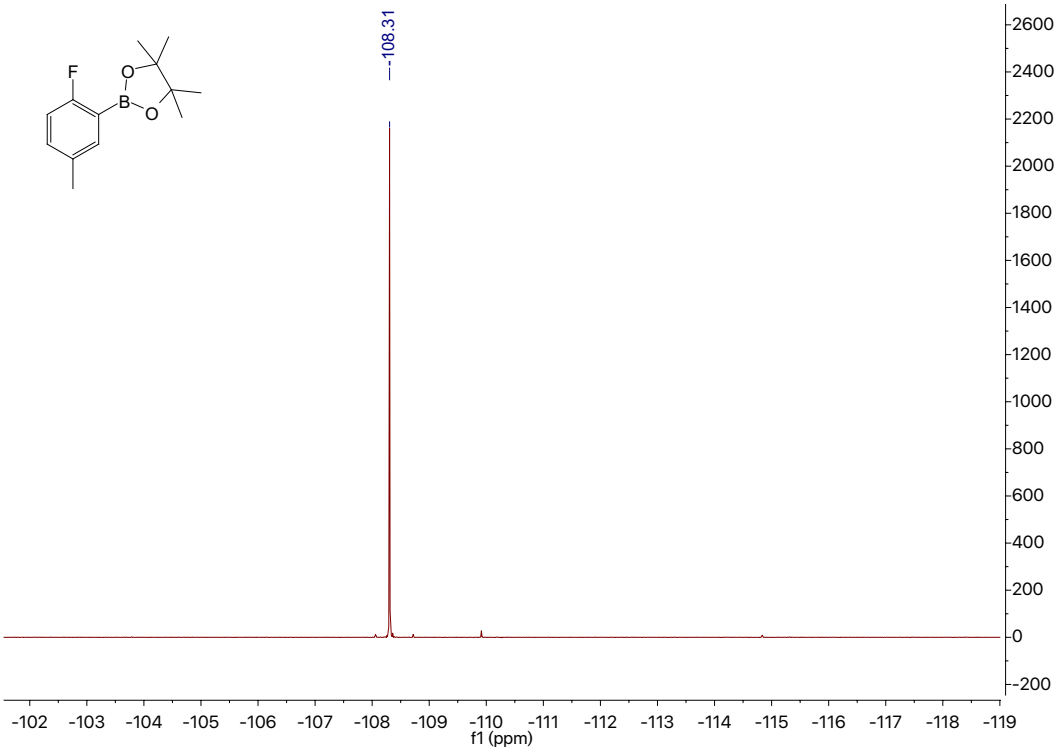
^{1}H (700 MHz, $CDCl_3$) — **61a**



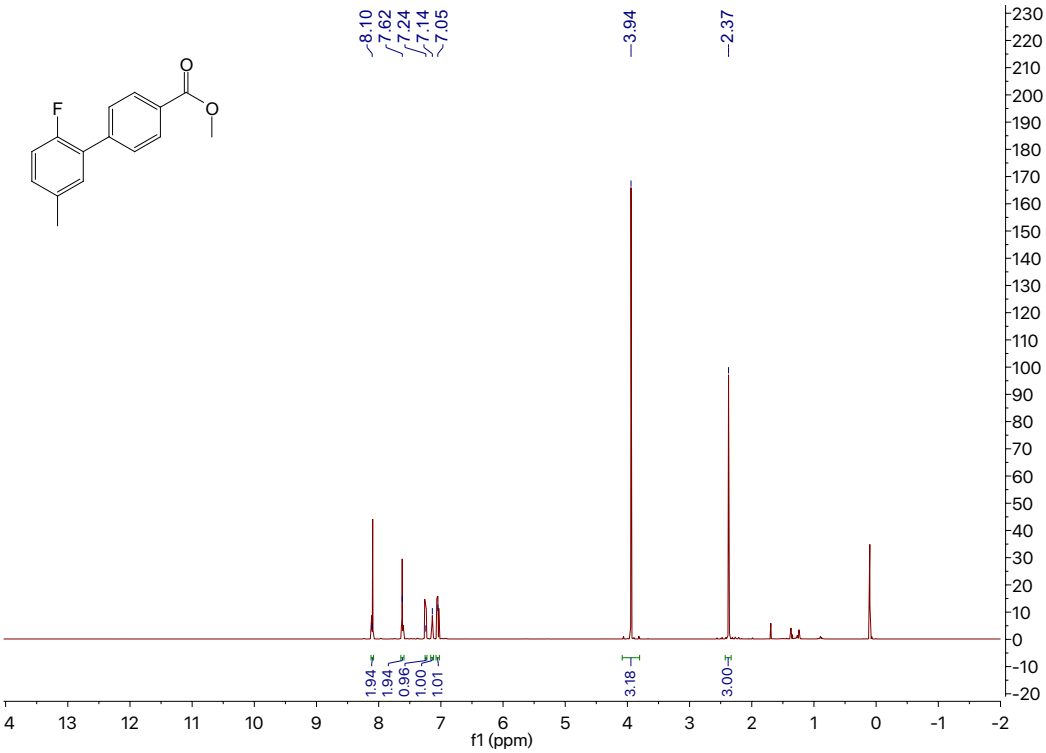
^{13}C (176 MHz, $CDCl_3$) — **61a**



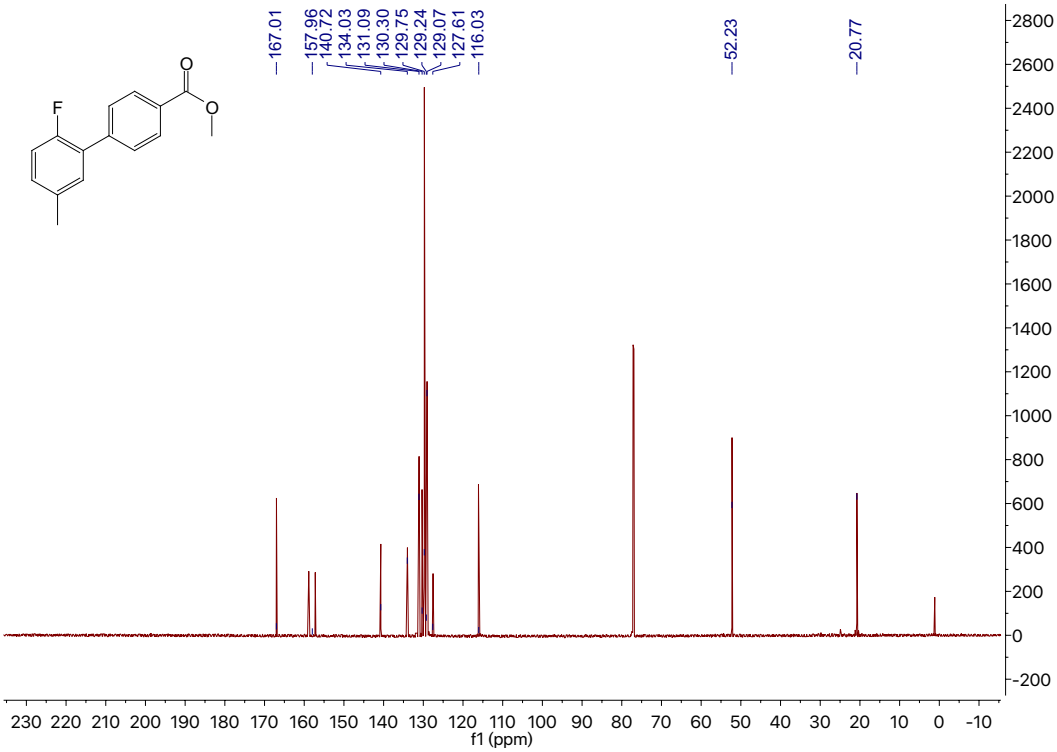
^{19}F (376 MHz, $CDCl_3$) — **61a**



^{1}H (599 MHz, $CDCl_3$) — **61c**



^{13}C (151 MHz, $CDCl_3$) — **61c**



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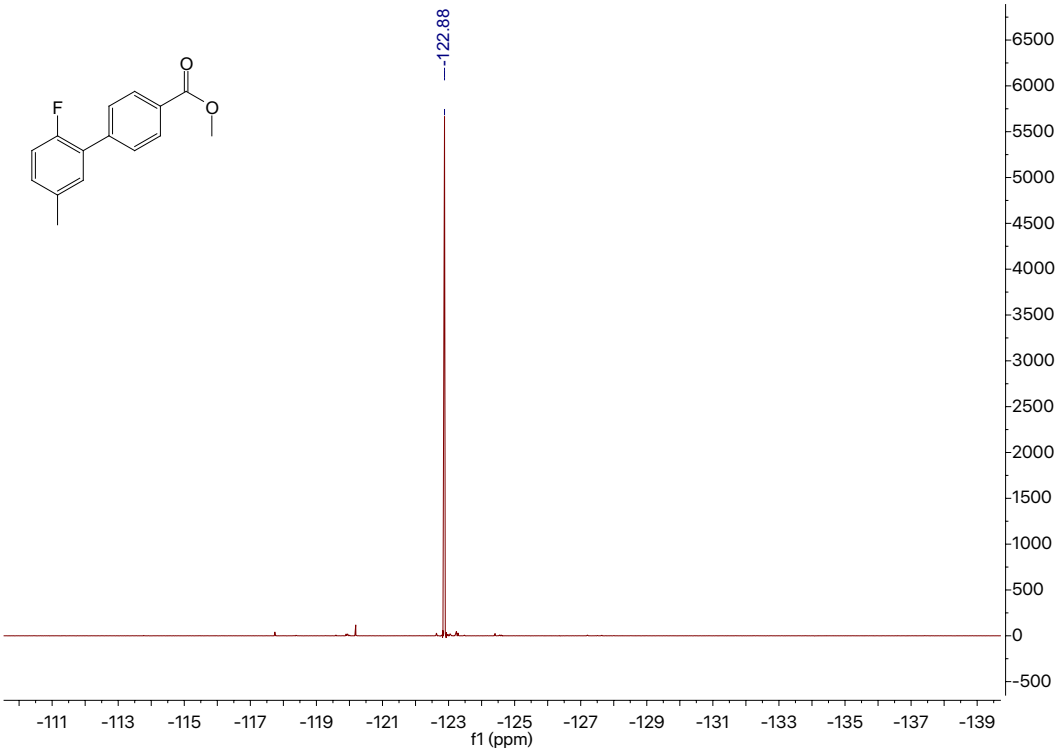
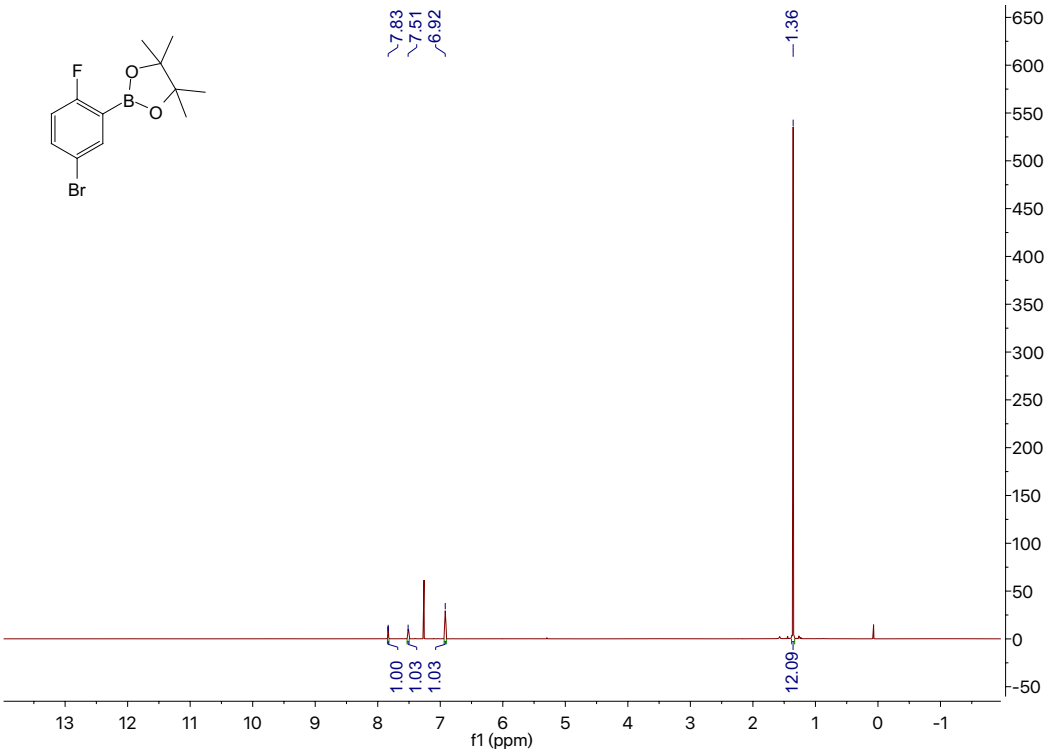
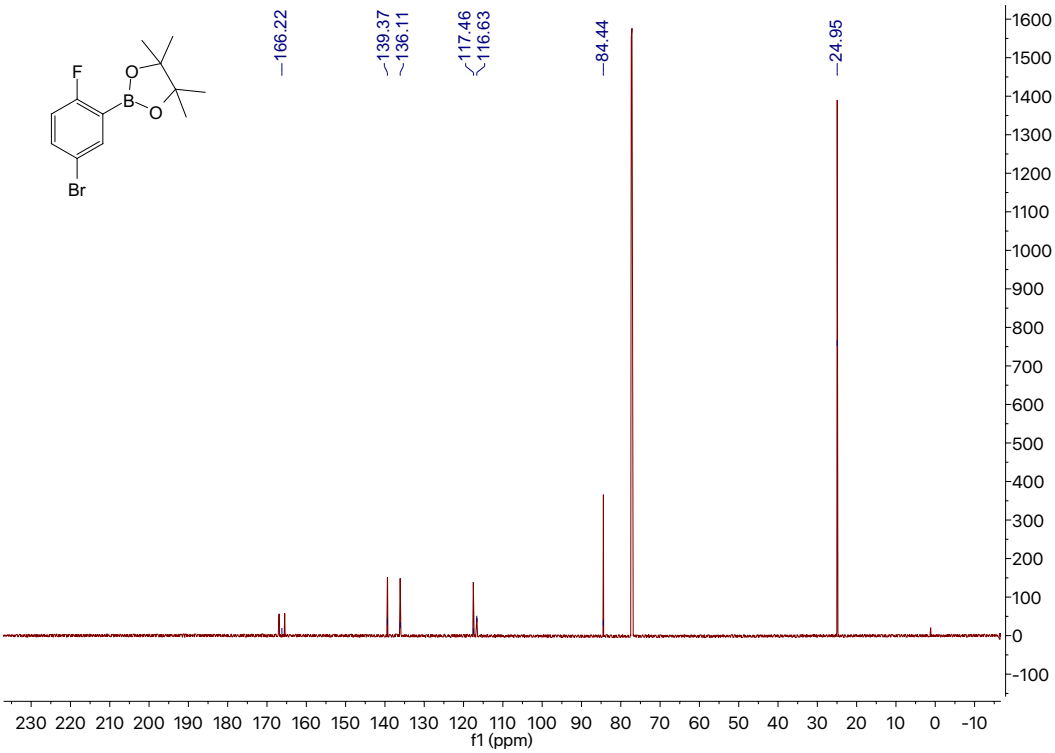


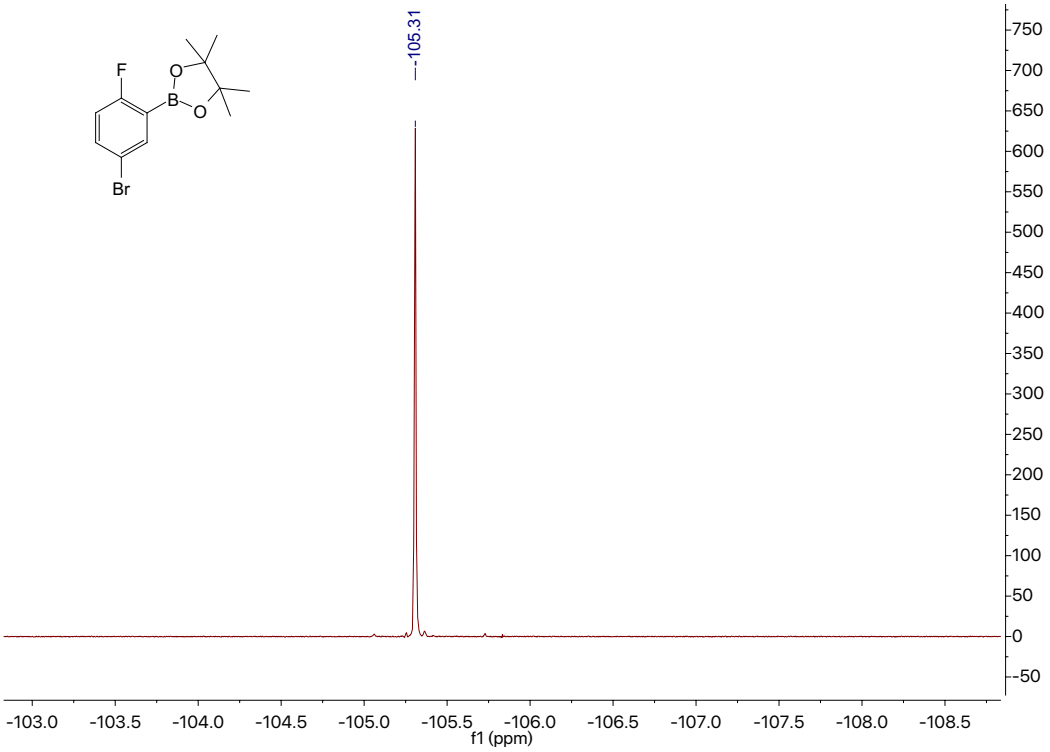
^{1}H (700 MHz, $CDCl_3$) — **62a**



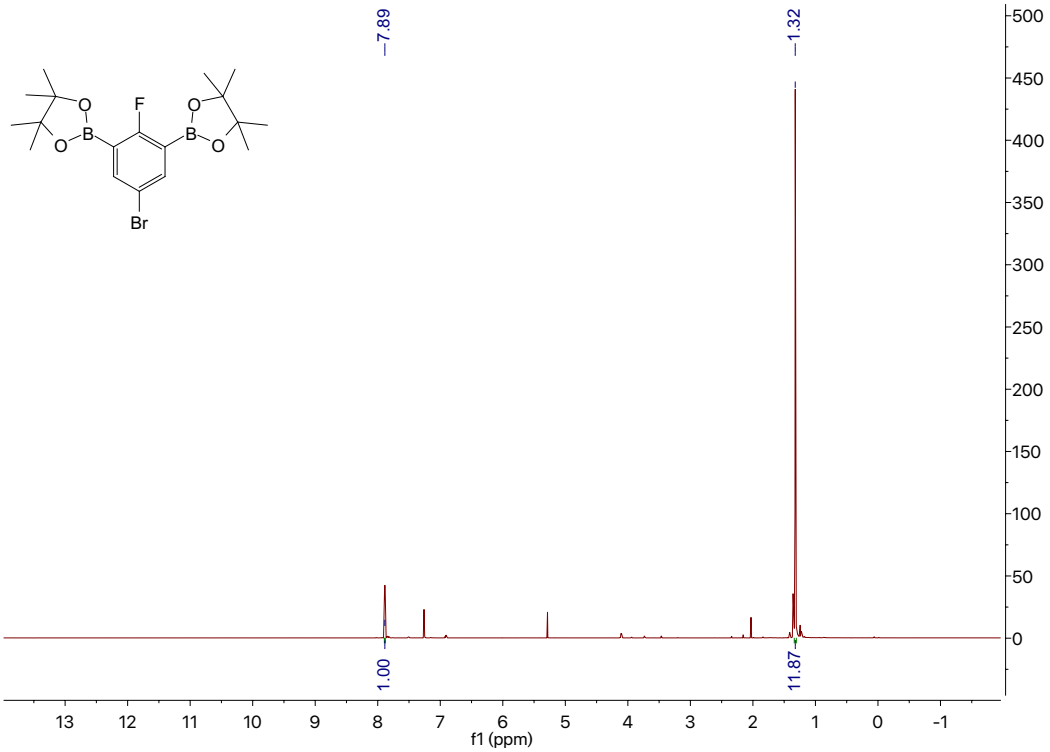
^{13}C (176 MHz, $CDCl_3$) — **62a**



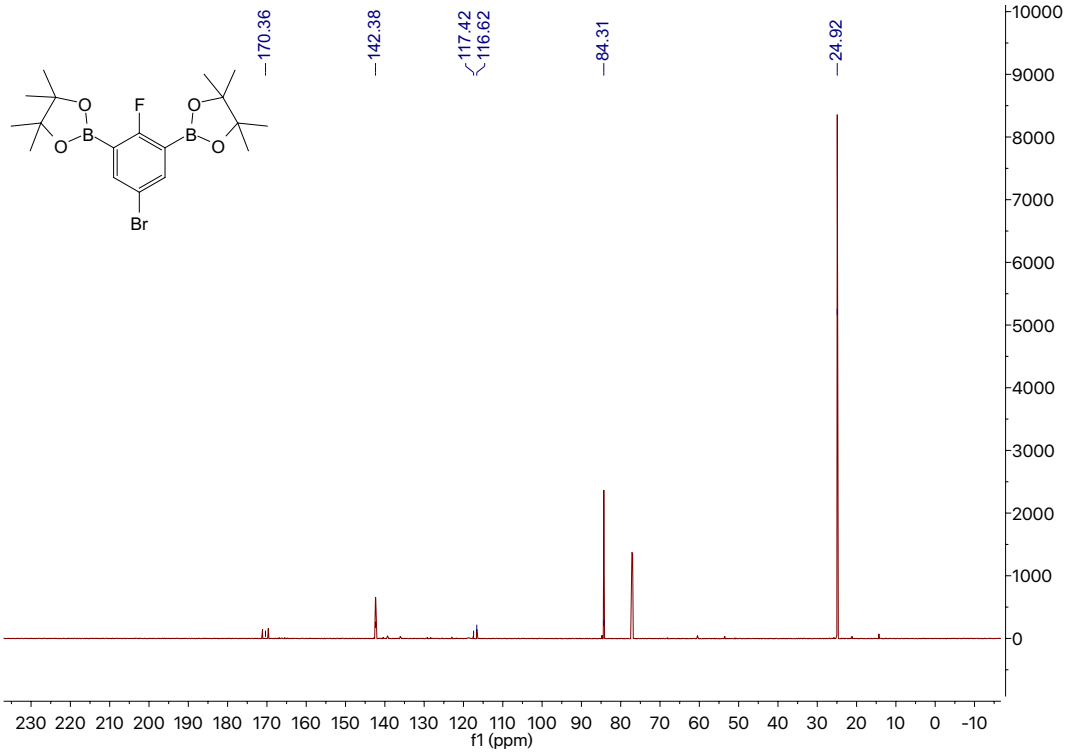
^{19}F (376 MHz, $CDCl_3$) — **62a**



^{1}H (700 MHz, $CDCl_3$) — **62b**



^{13}C (176 MHz, $CDCl_3$) — **62b**



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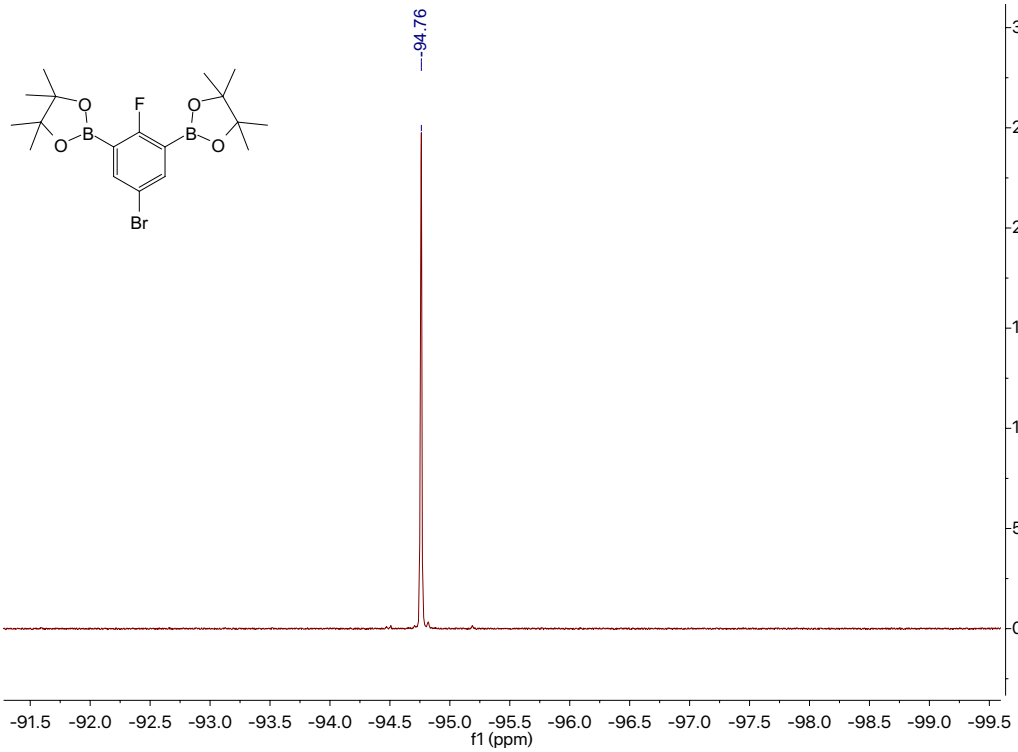

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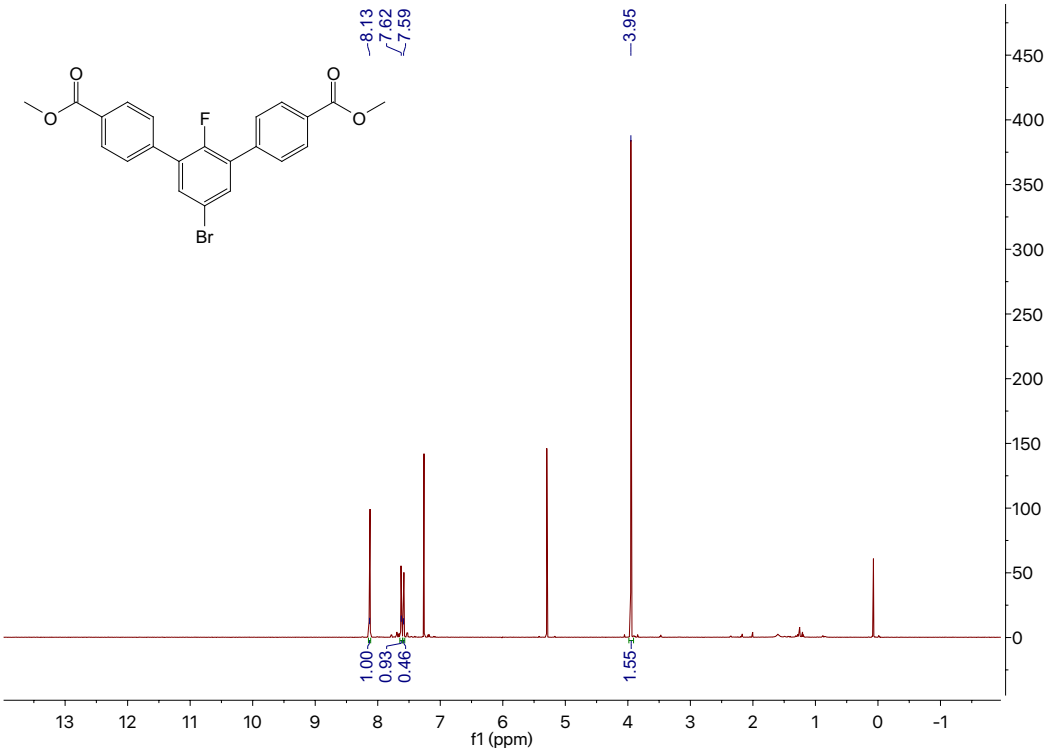

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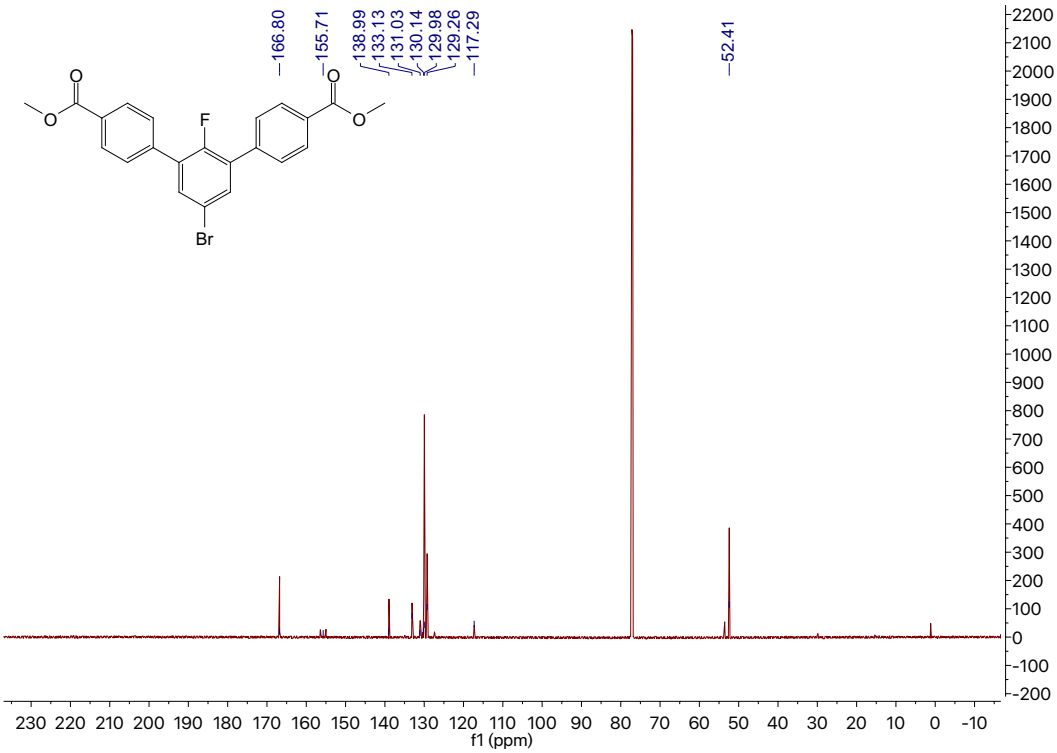

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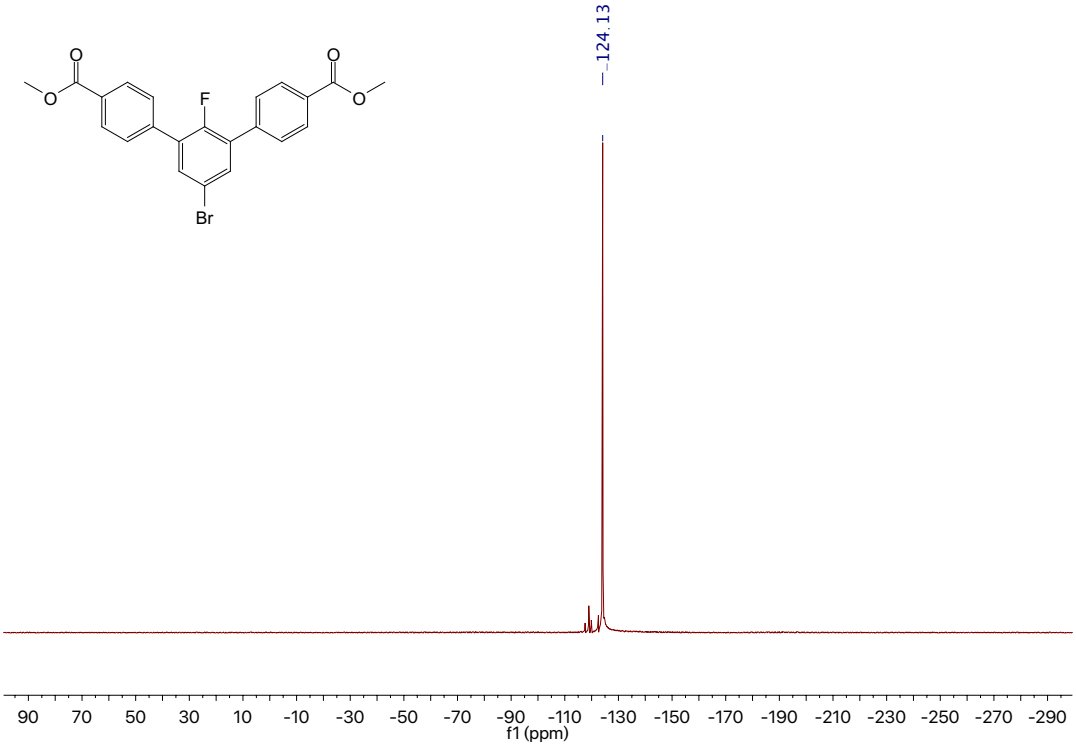
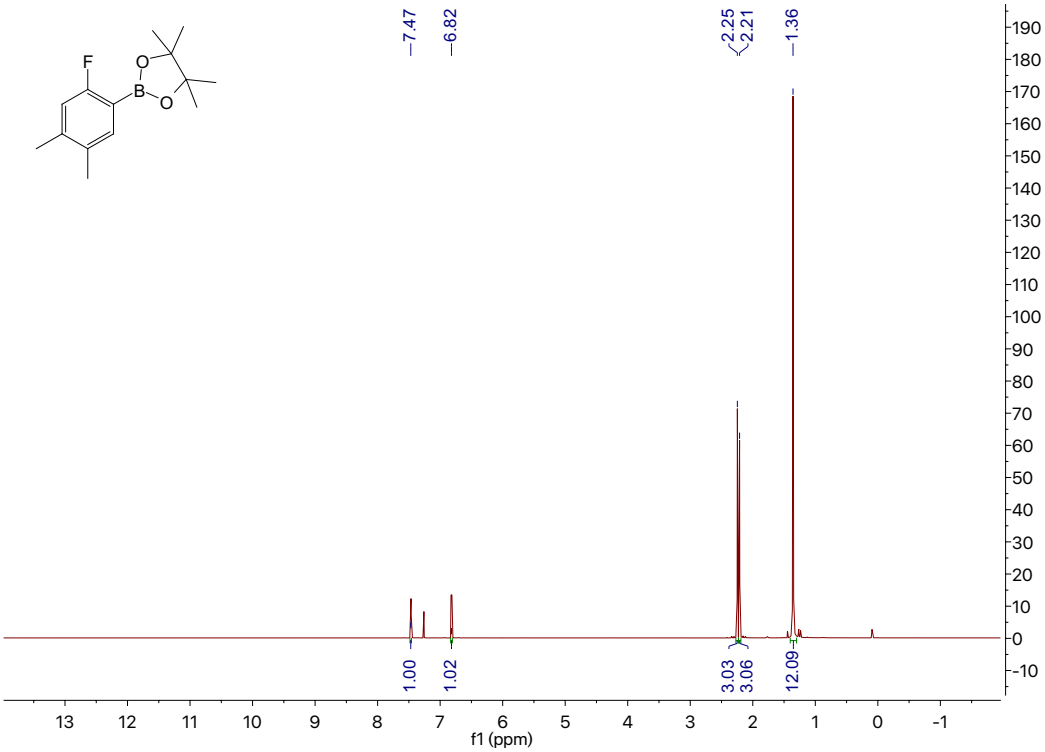


^{1}H (700 MHz, $CDCl_3$) — **64a**



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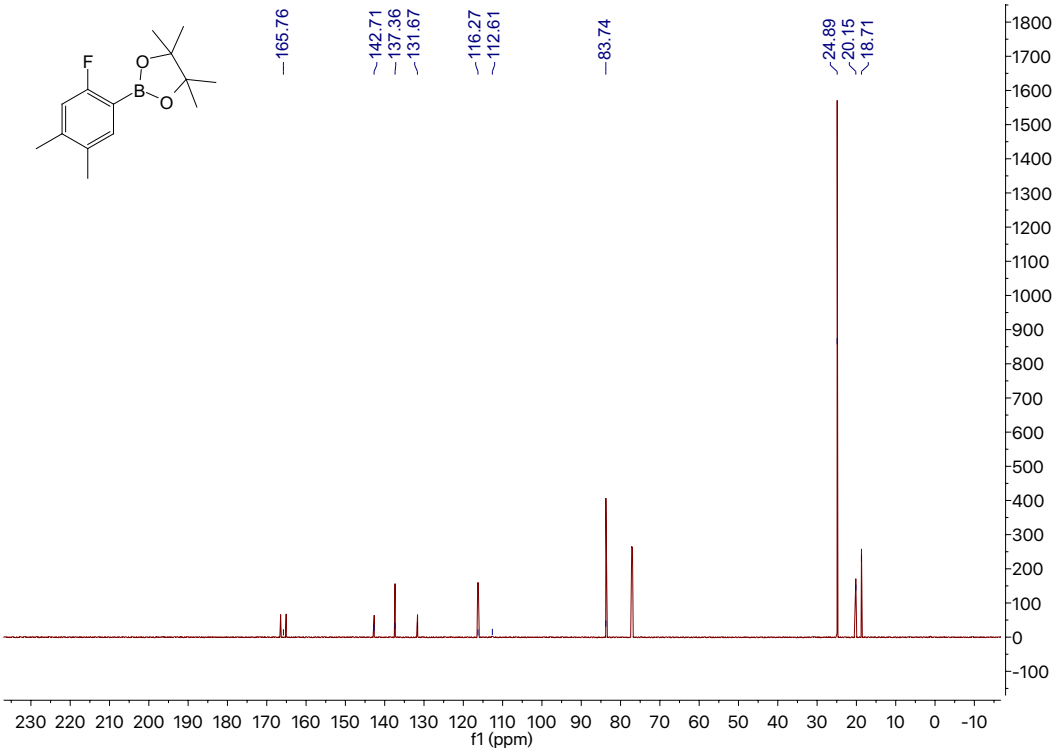

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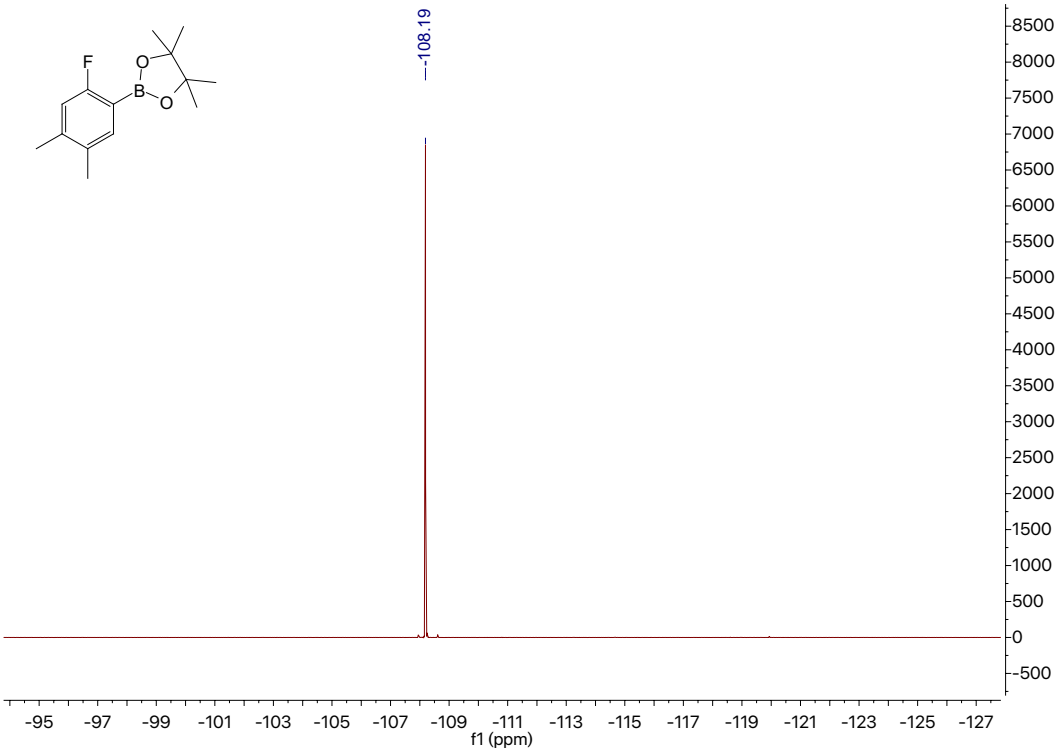
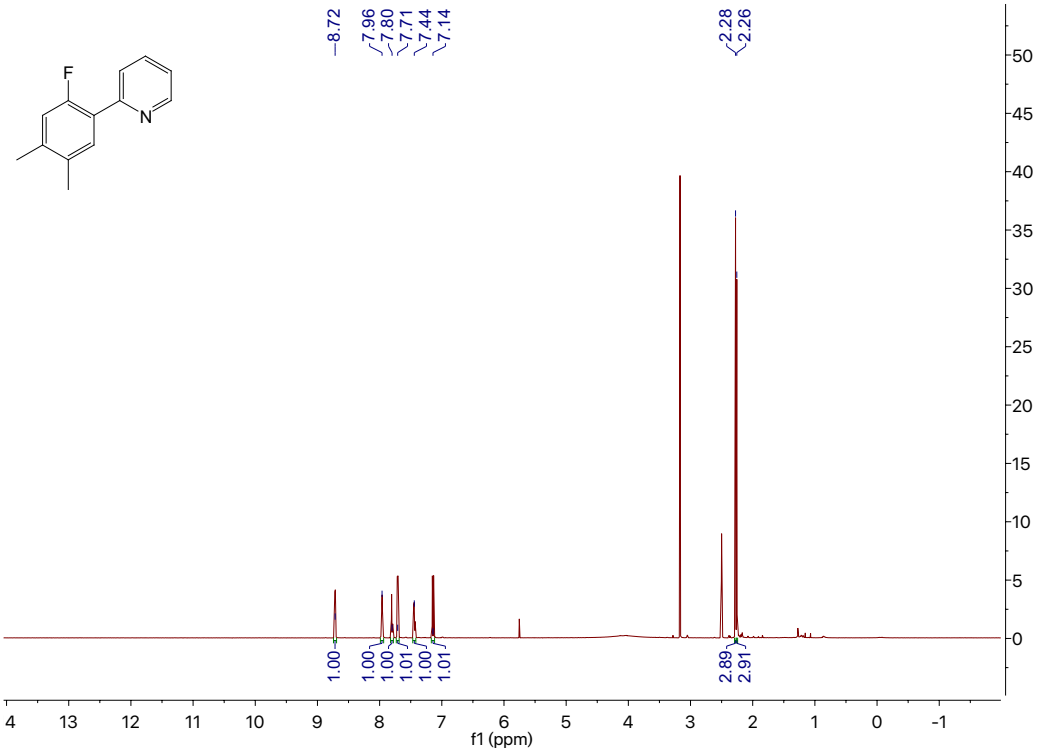
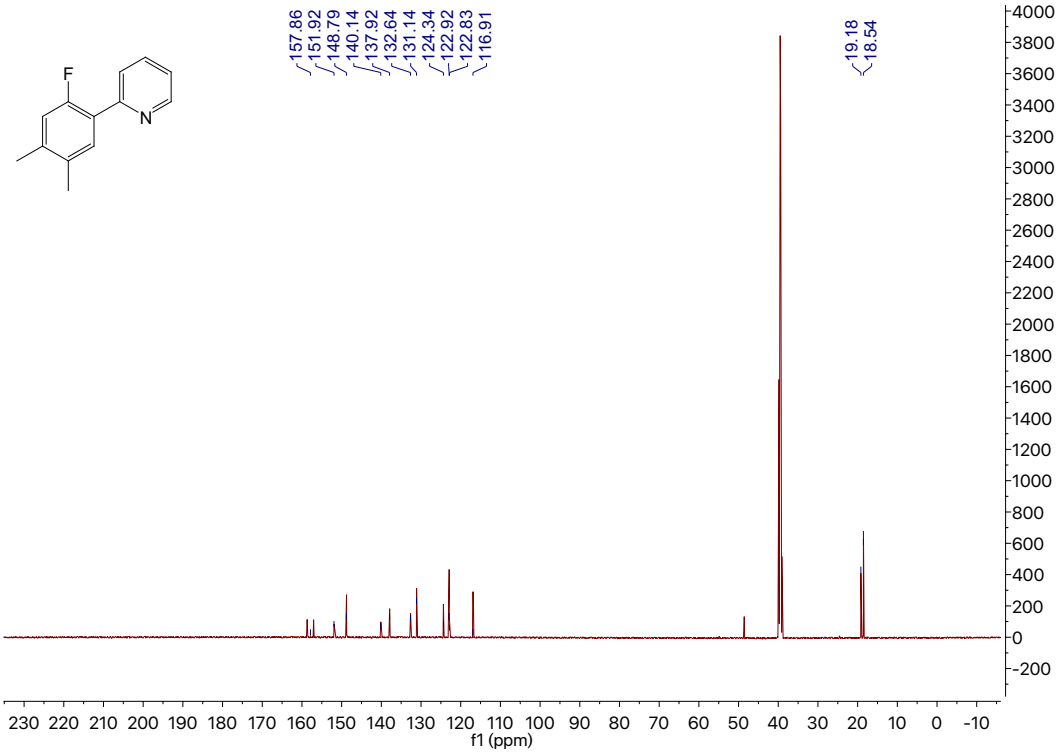


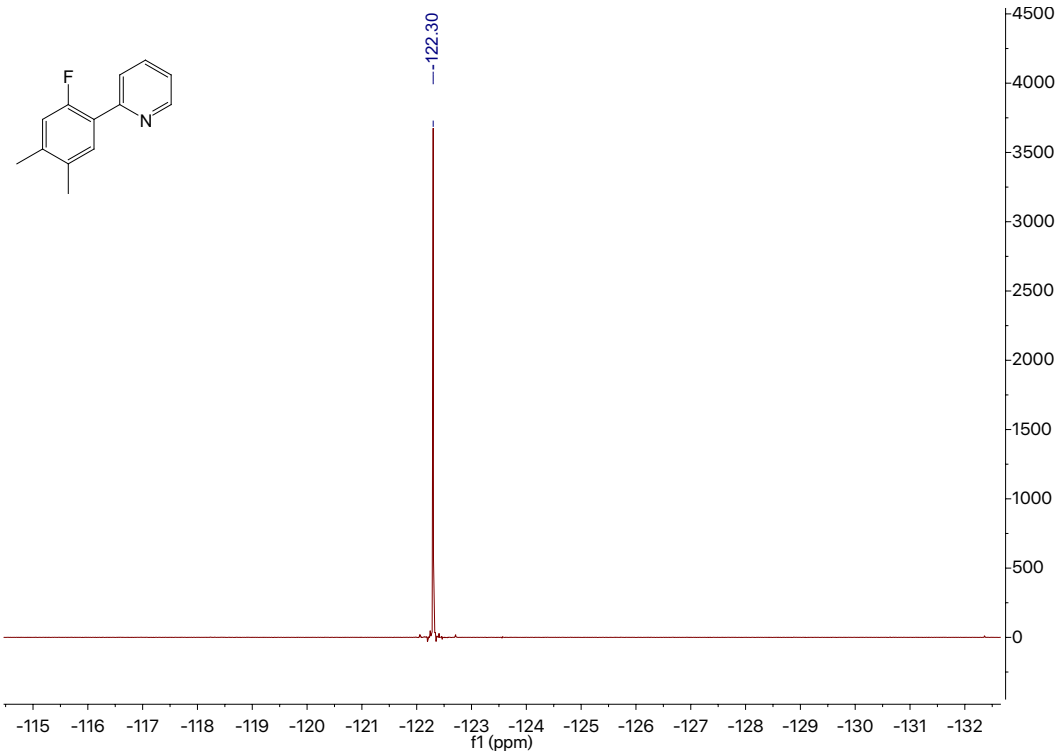
^{1}H (599 MHz, DMSO) — **64b**



^{13}C (151 MHz, DMSO) — **64b**



^{19}F (376 MHz, DMSO) — **64b**



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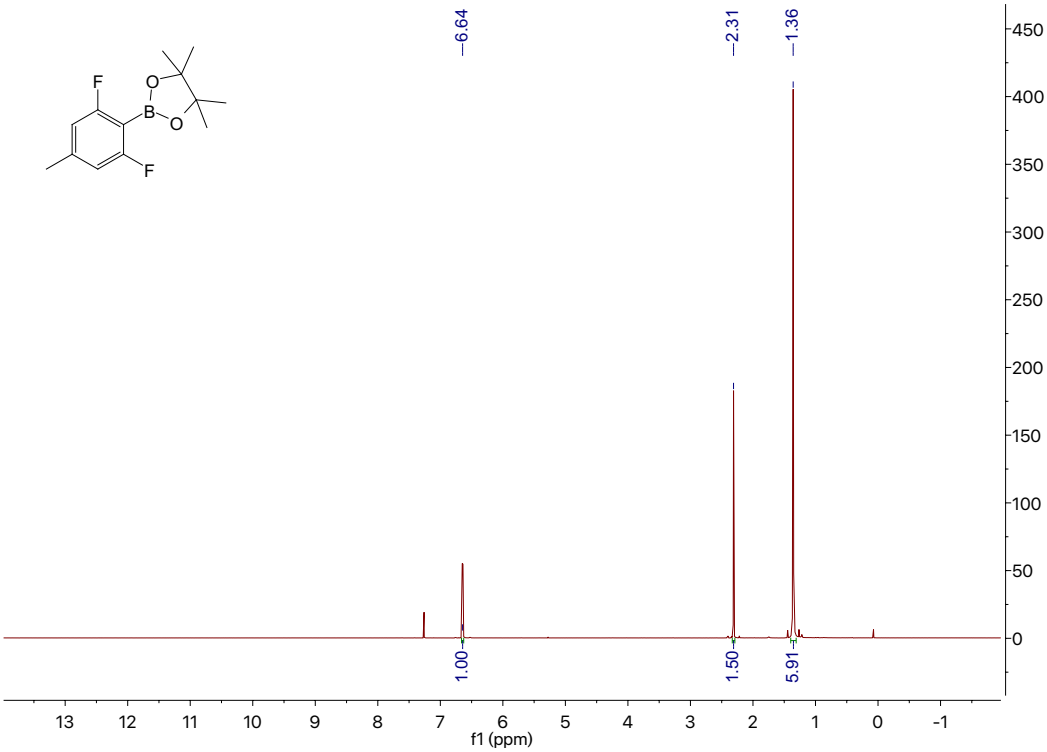

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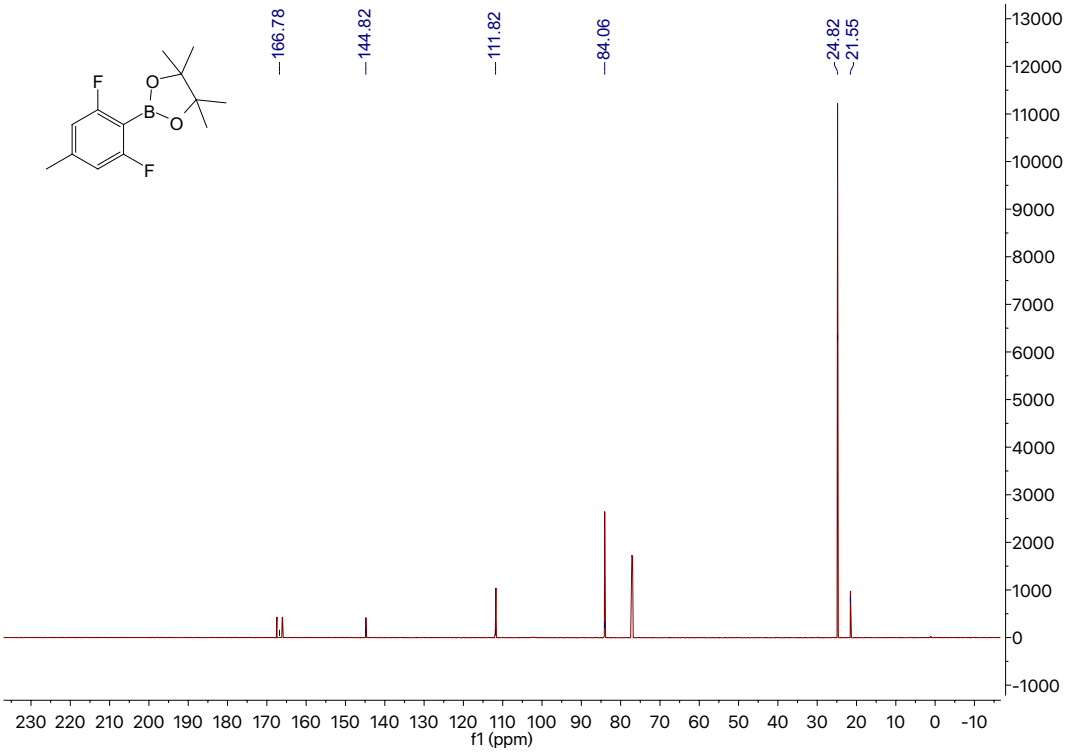

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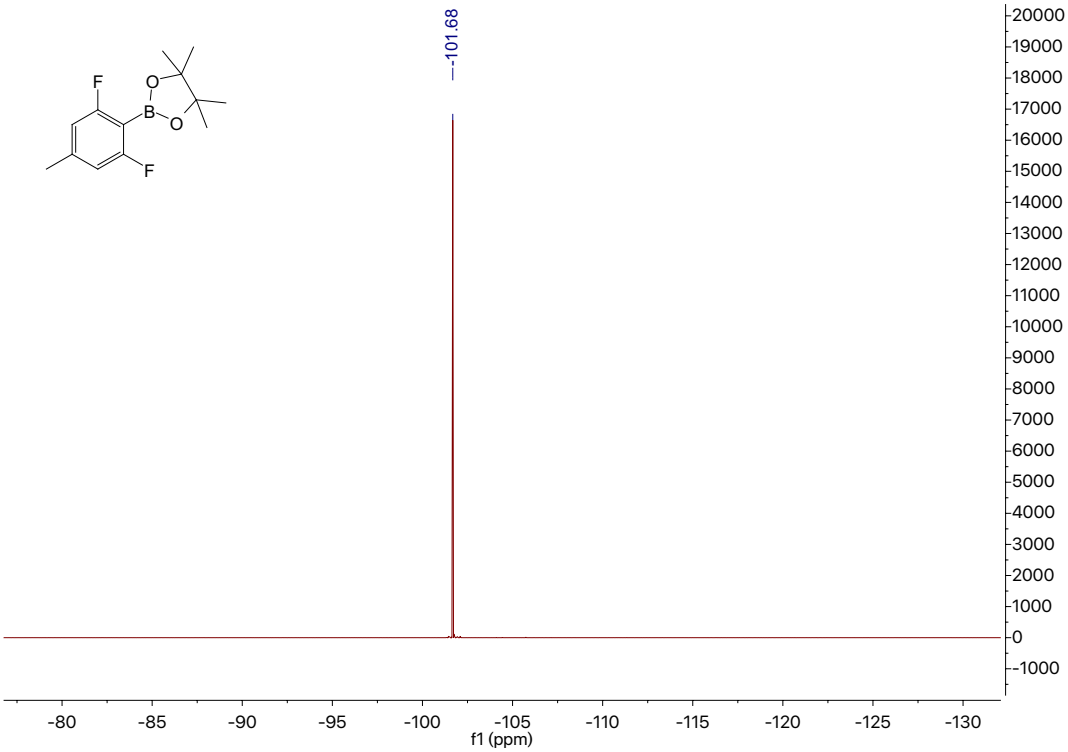

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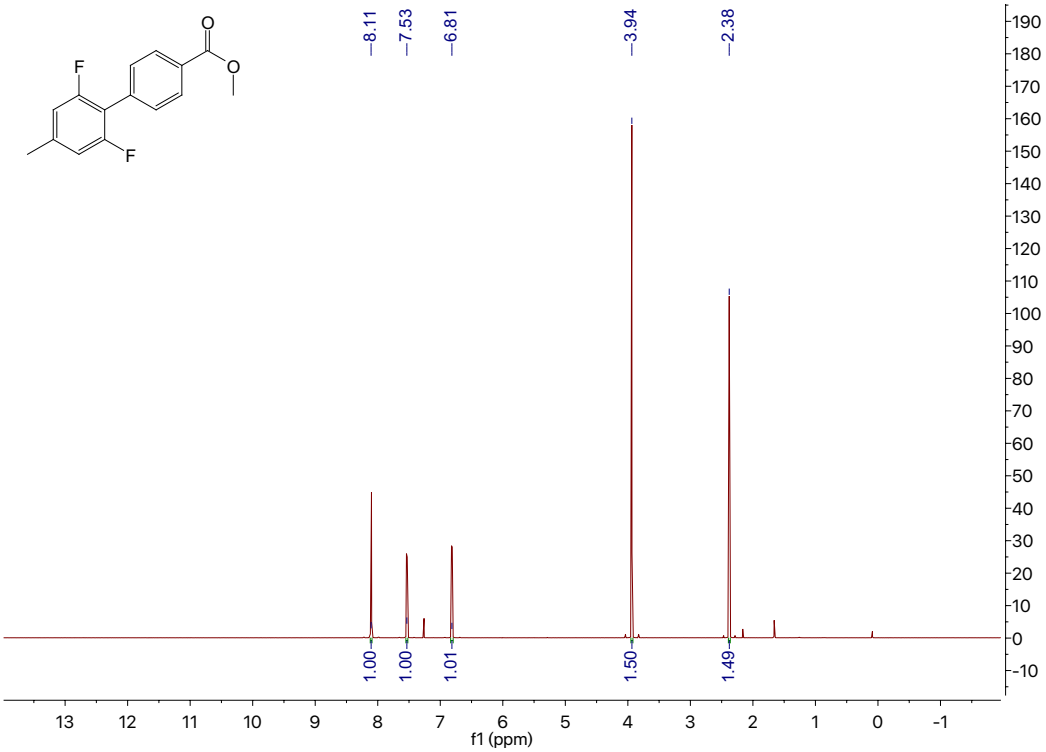

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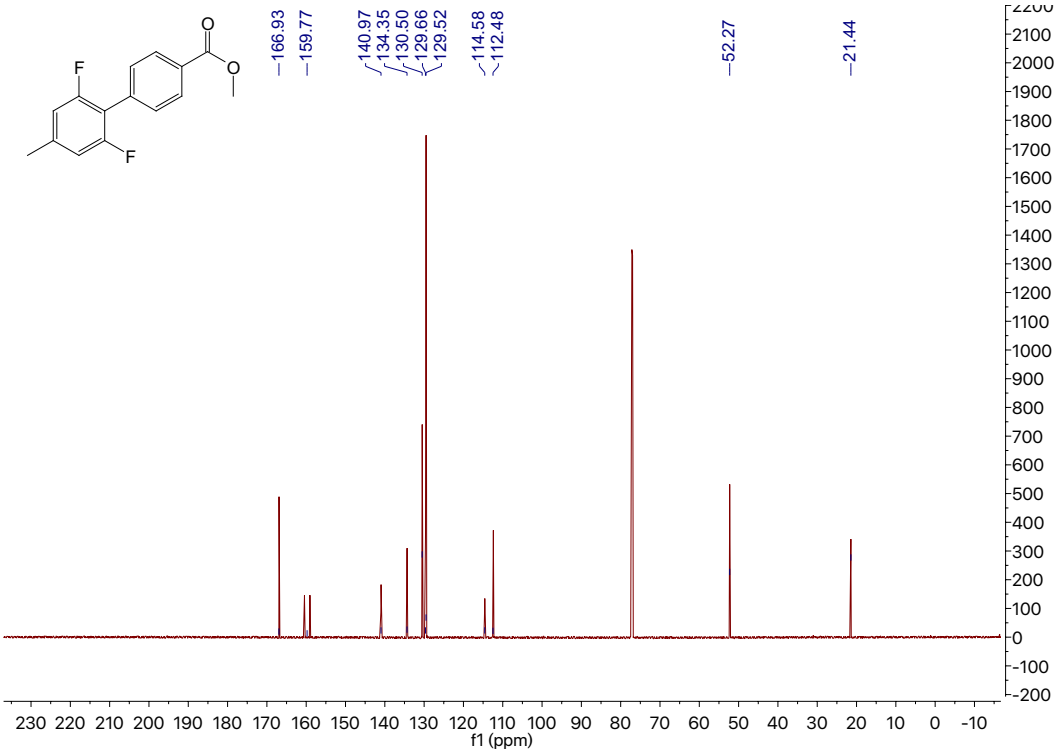

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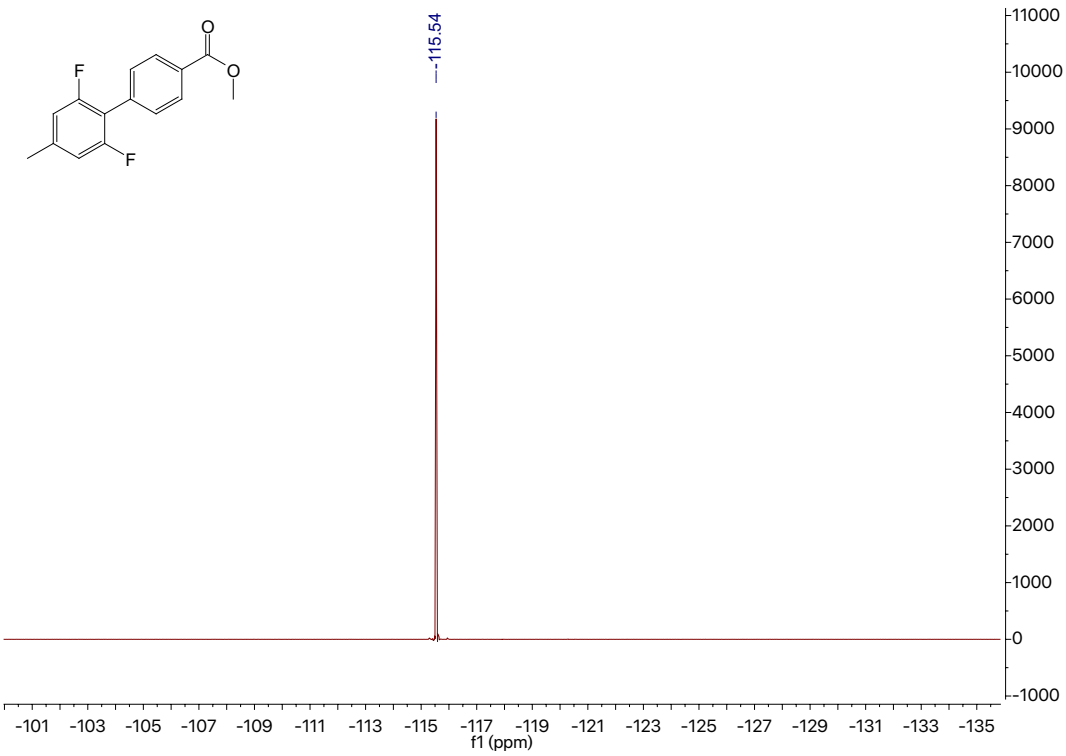
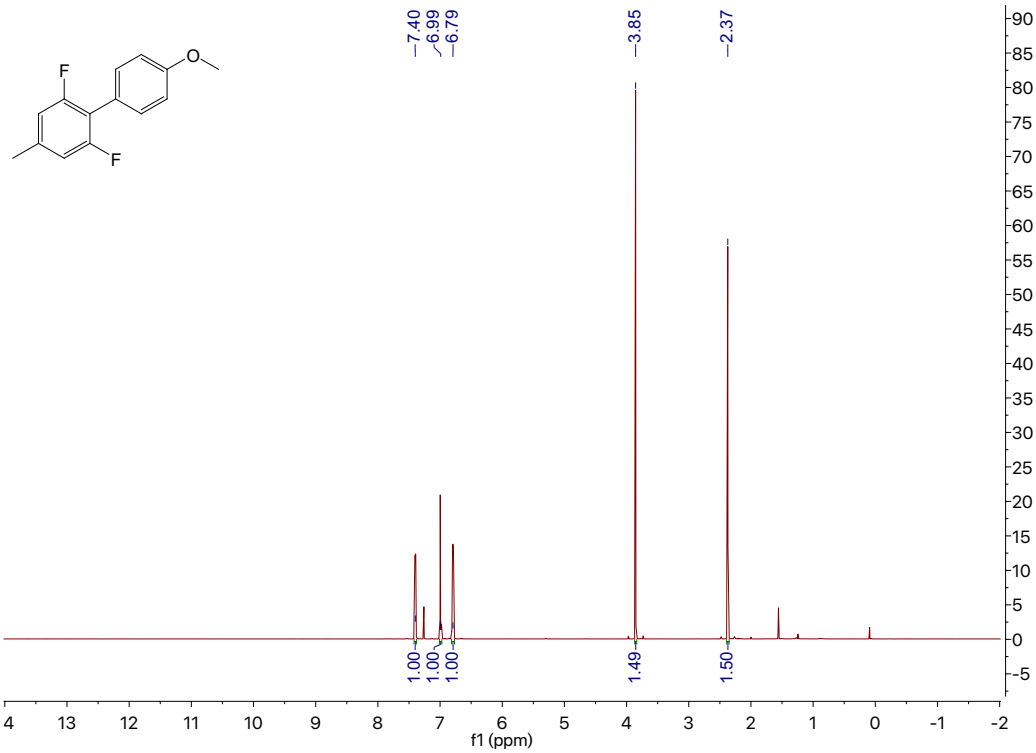
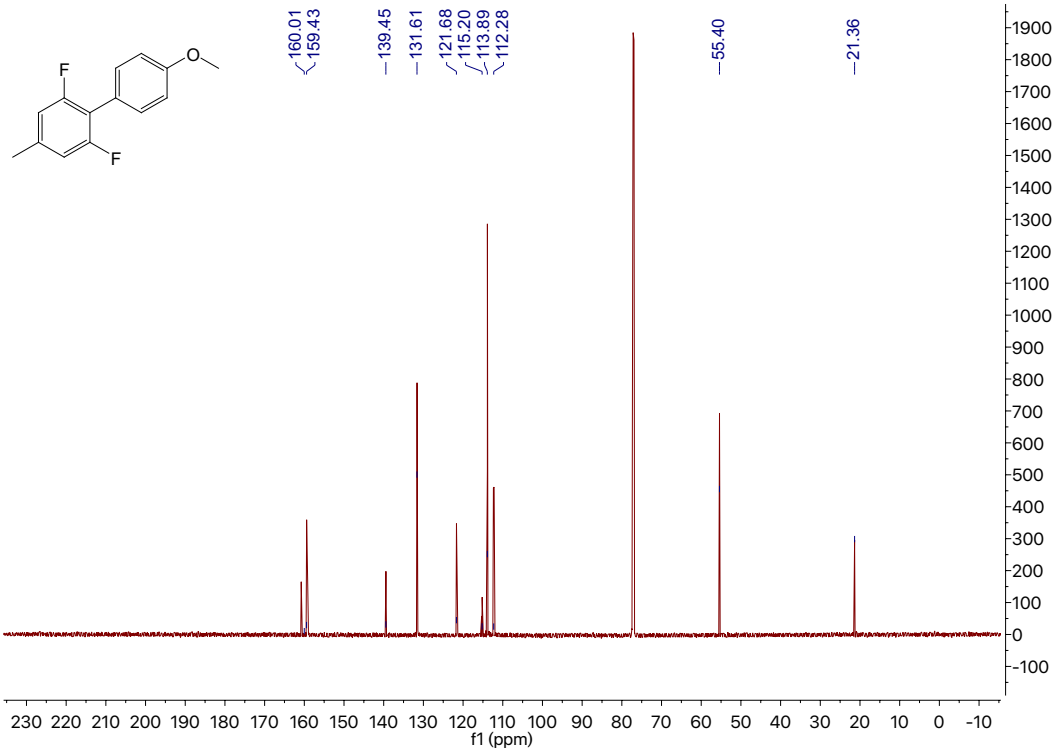


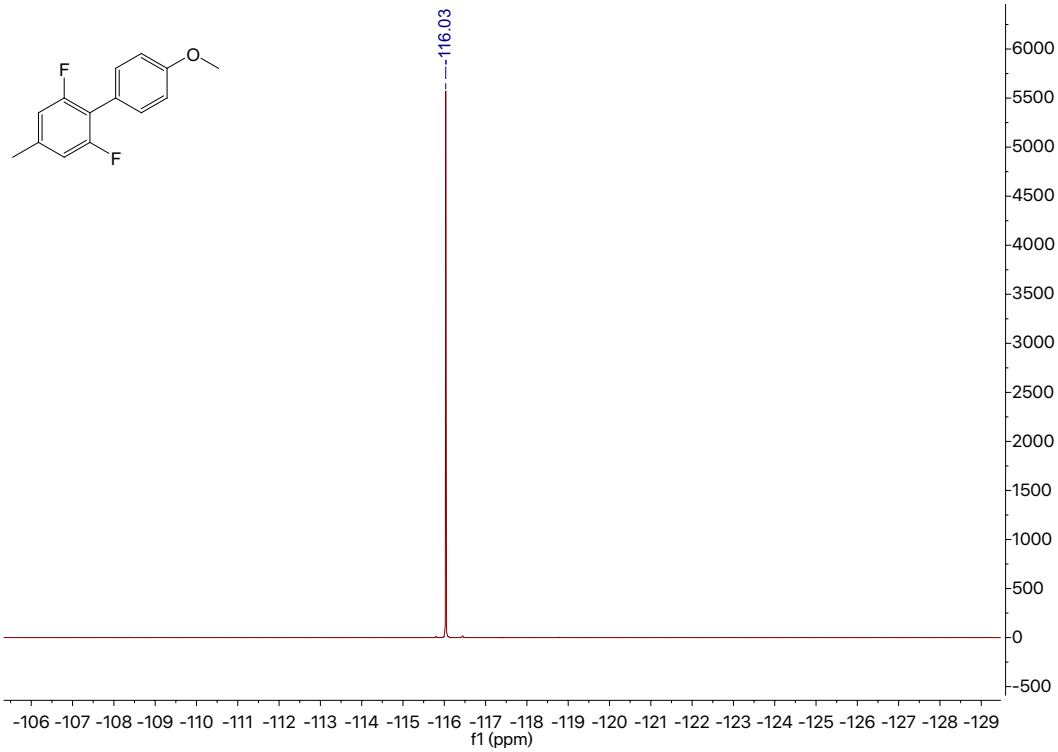
^{1}H (599 MHz, $CDCl_3$) — **66c**



^{13}C (151 MHz, $CDCl_3$) — **66c**



^{19}F (376 MHz, $CDCl_3$) — **66c**



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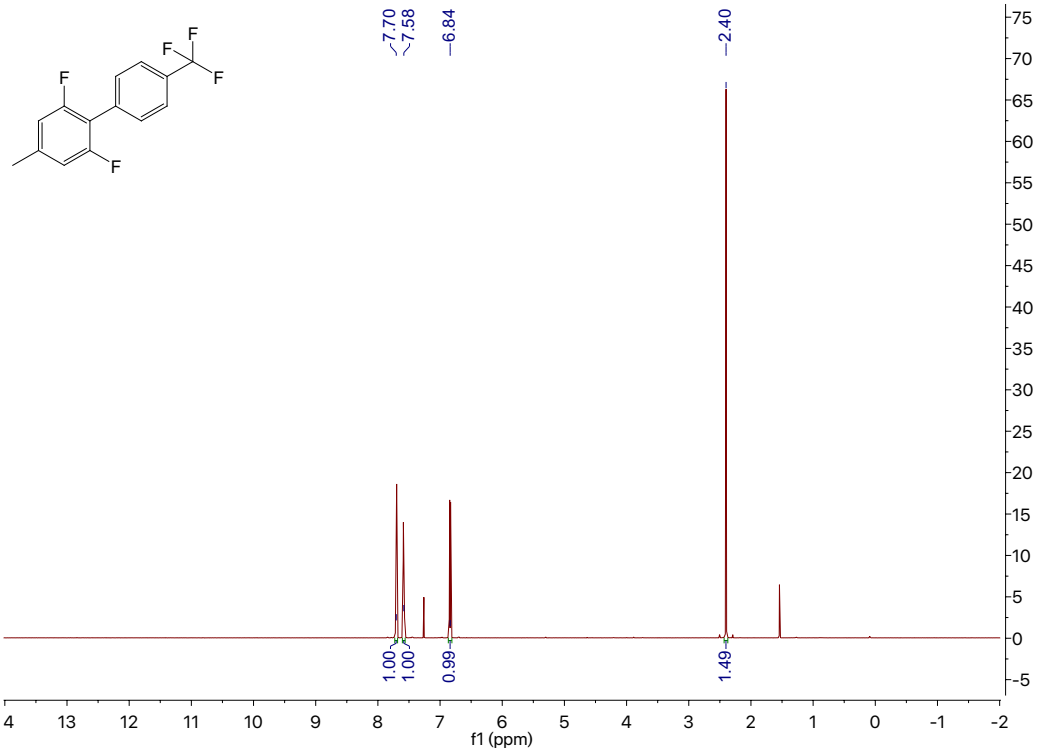

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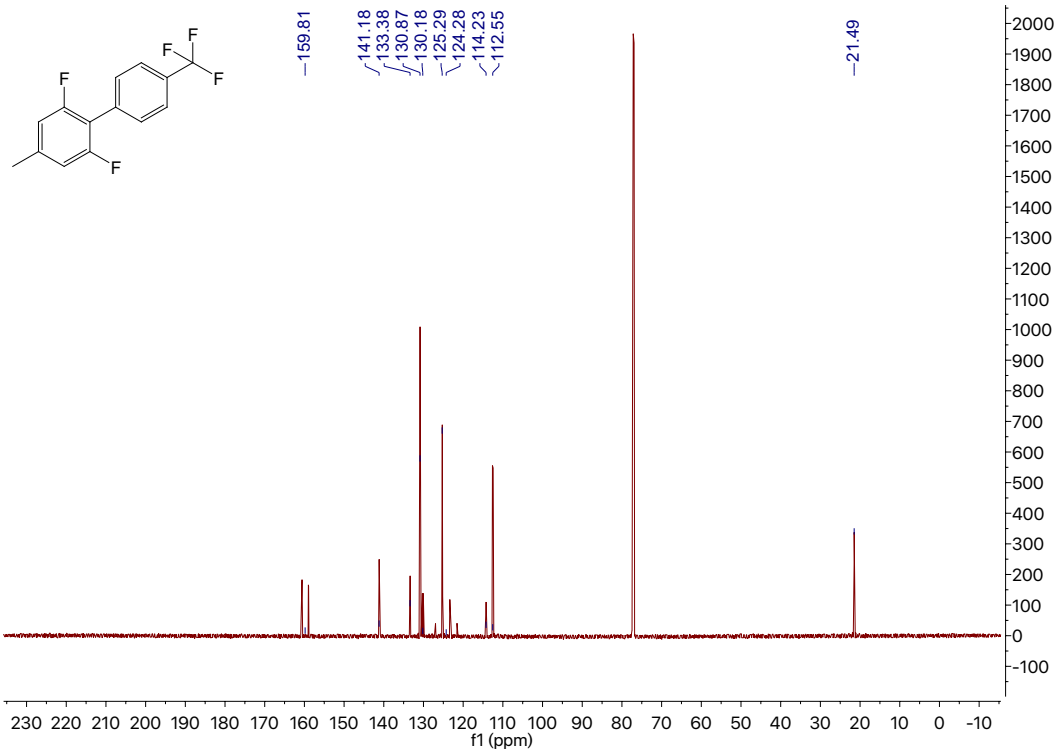

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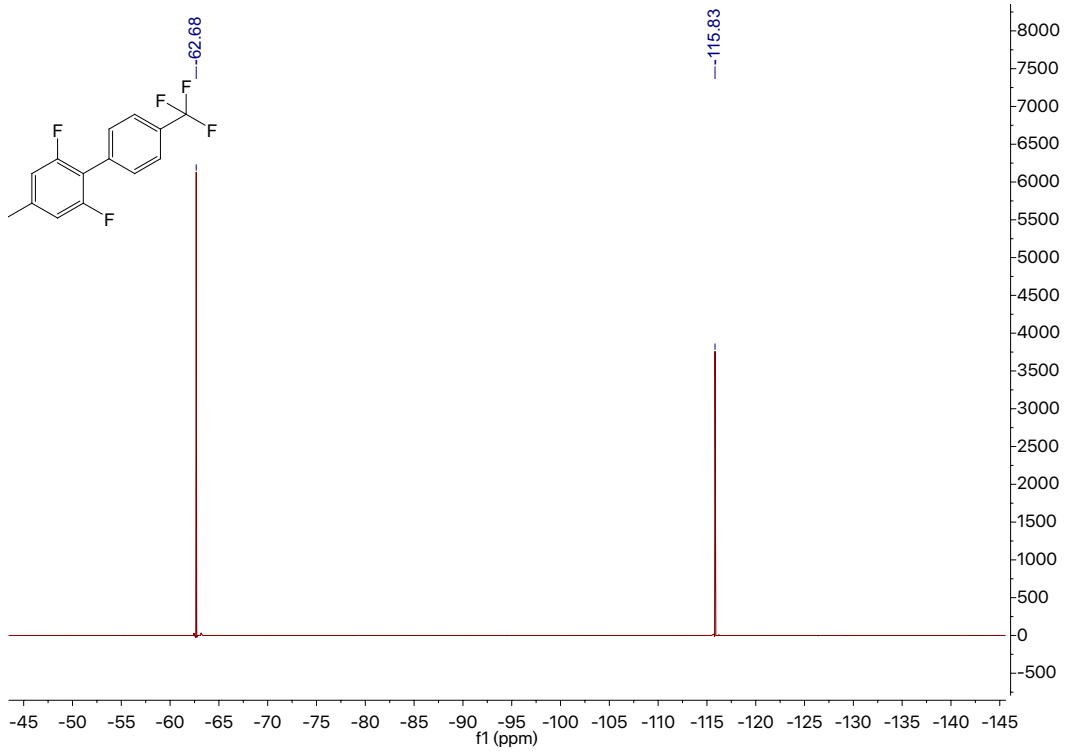
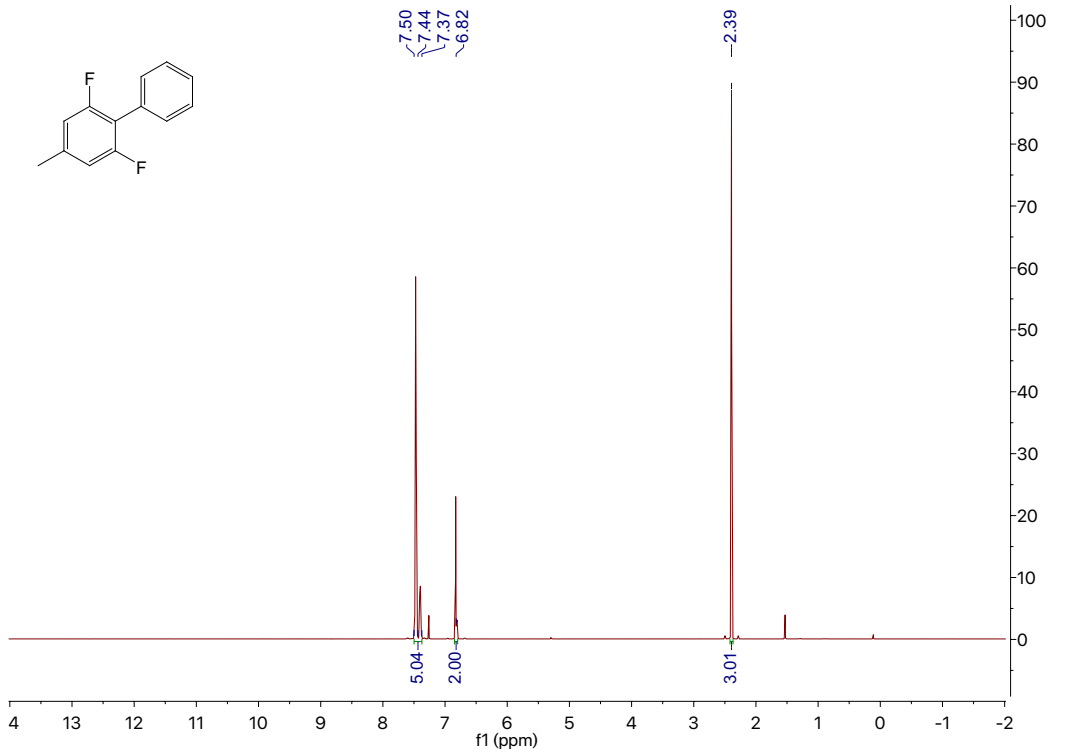


^{1}H (599 MHz, $CDCl_3$) — **66e**



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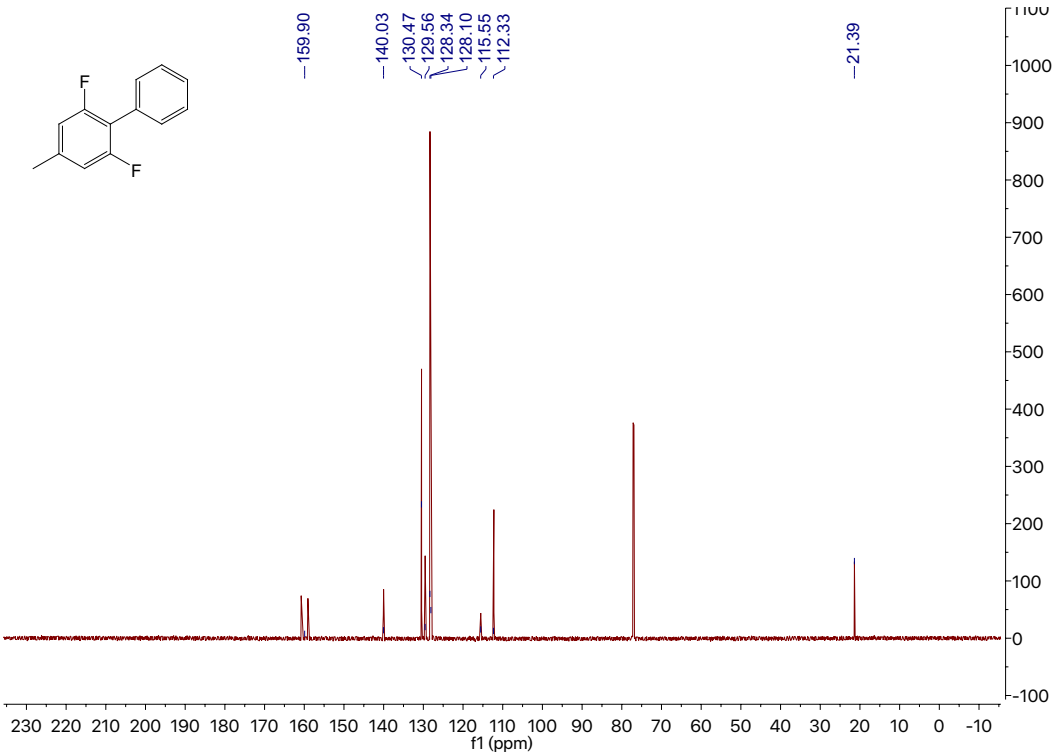
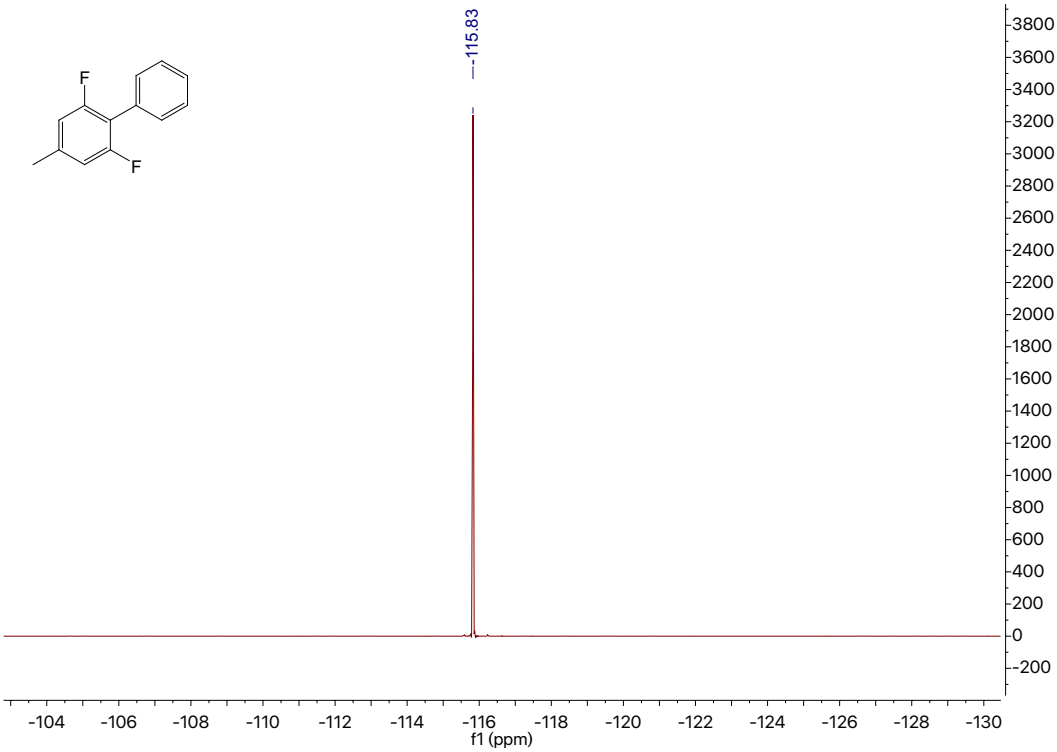
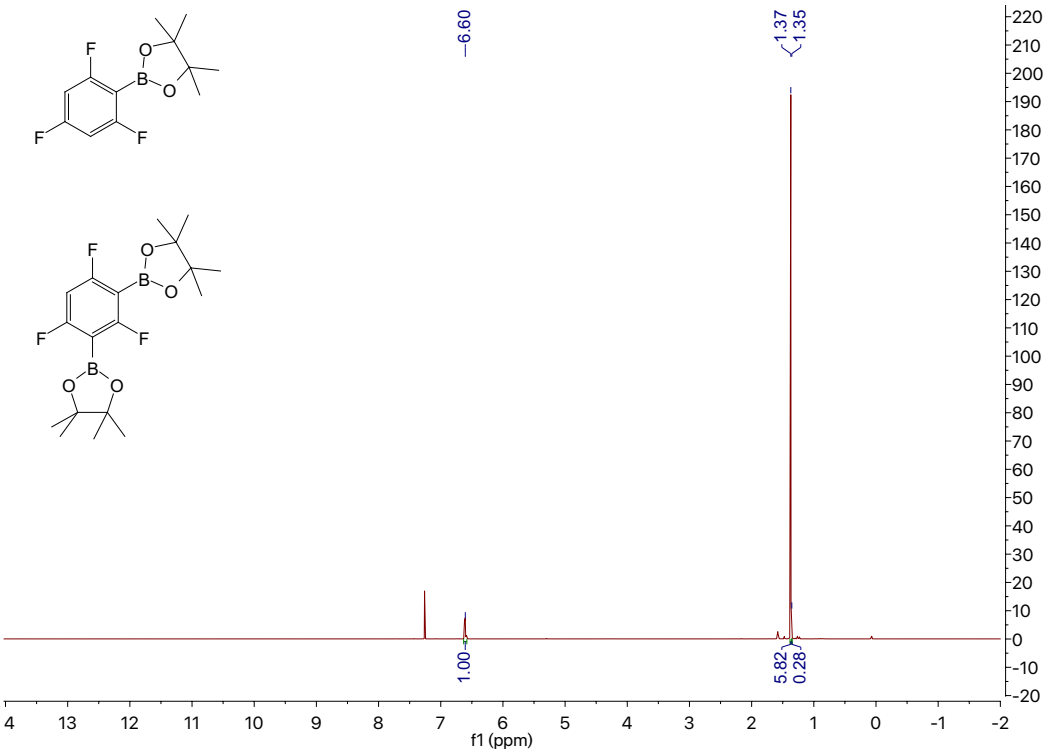


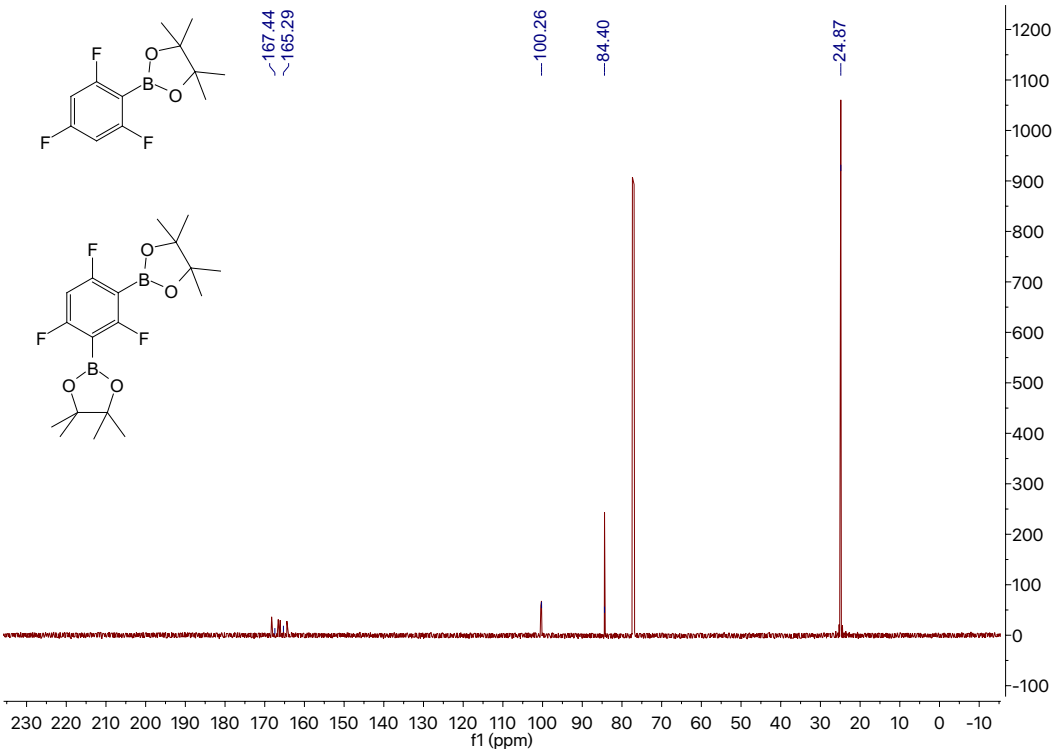
^{19}F (376 MHz, $CDCl_3$) — **66e**



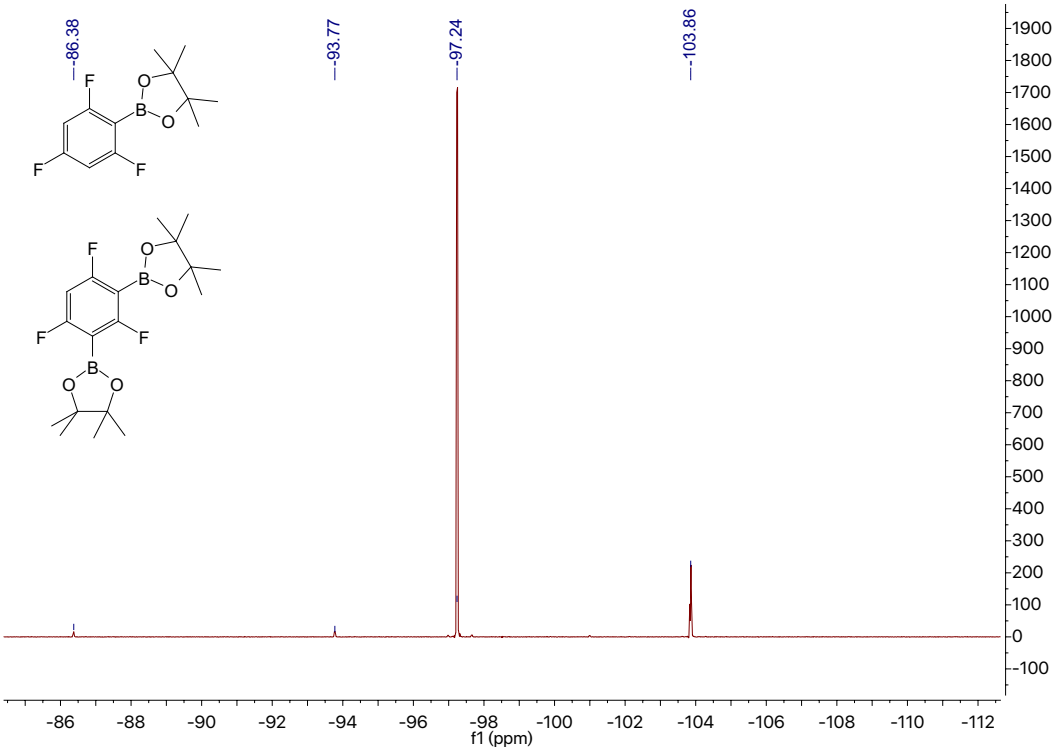
^{1}H (599 MHz, $CDCl_3$) — mixture of **67a** and **67b** (98 : 2)



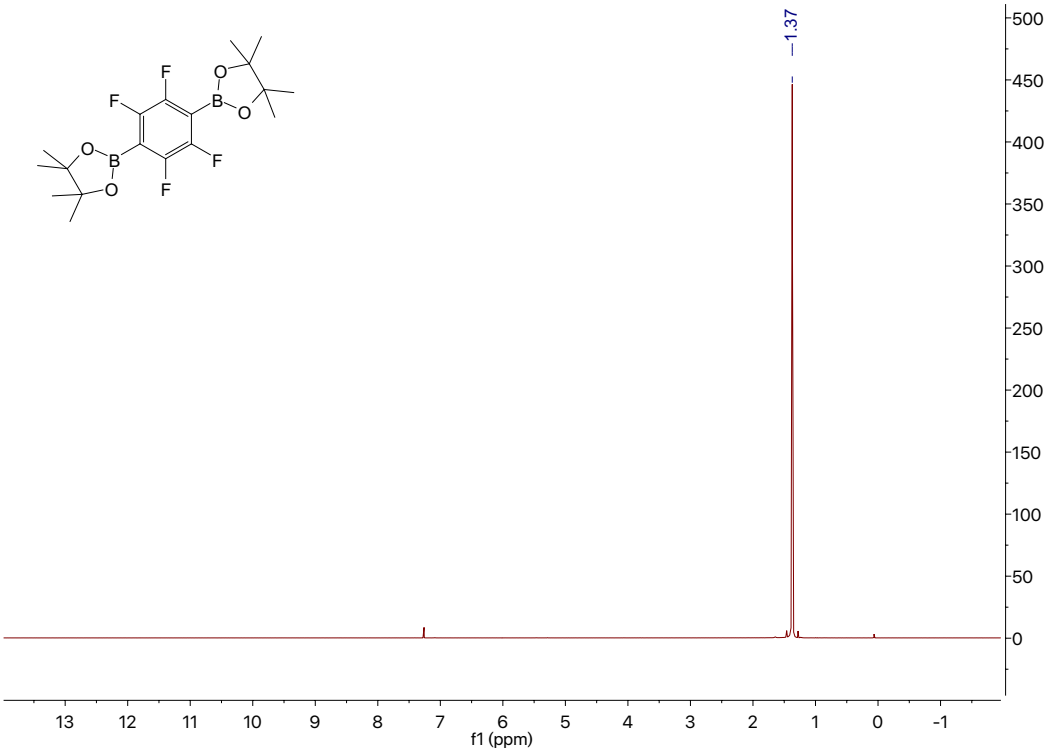
^{13}C (151 MHz, $CDCl_3$) — mixture of **67a** and **67b** (98 : 2)



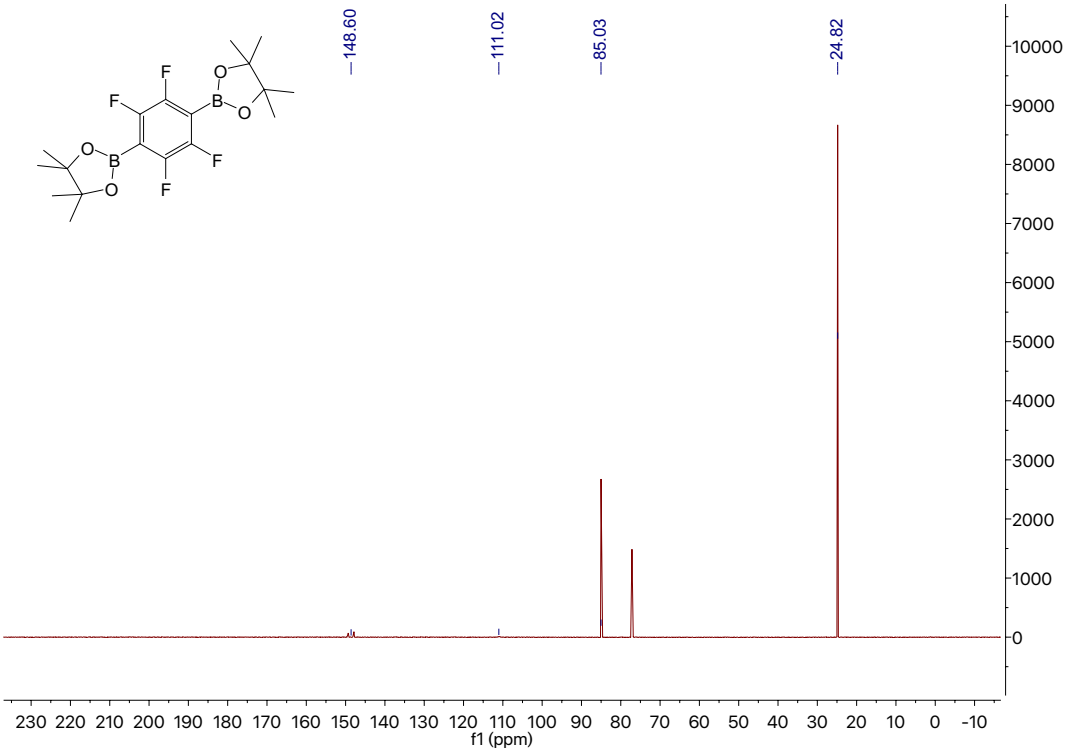
^{19}F (376 MHz, $CDCl_3$) — mixture of **67a** and **67b** (98 : 2)



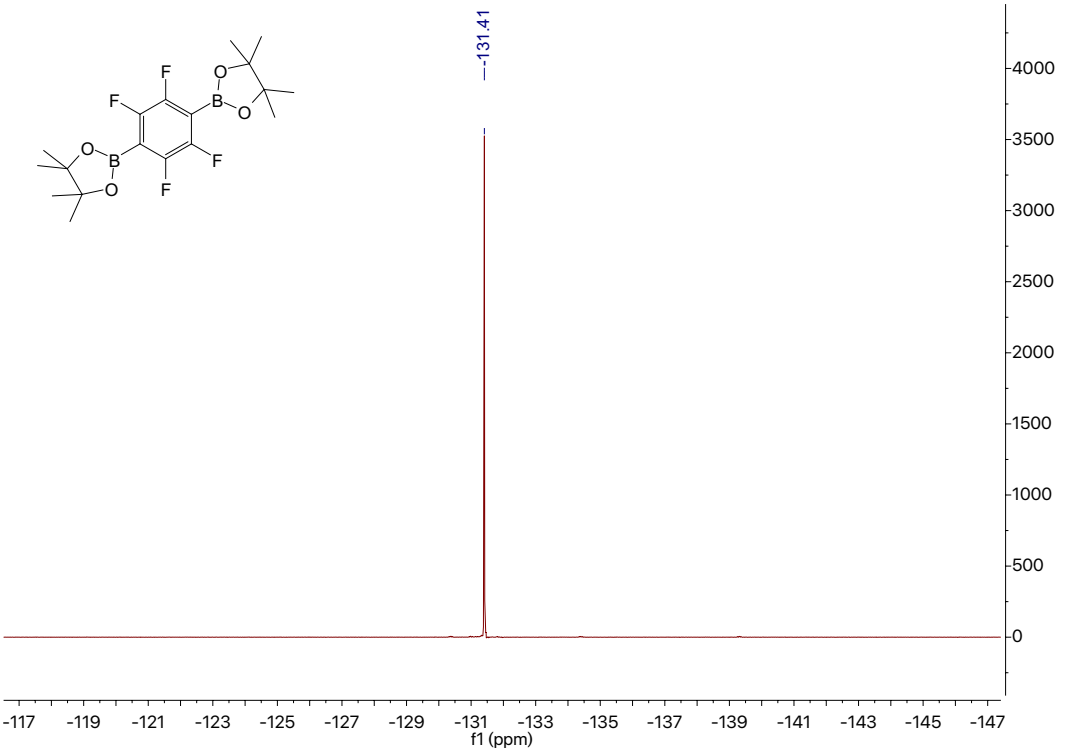
^{1}H (700 MHz, $CDCl_3$) — **68b**



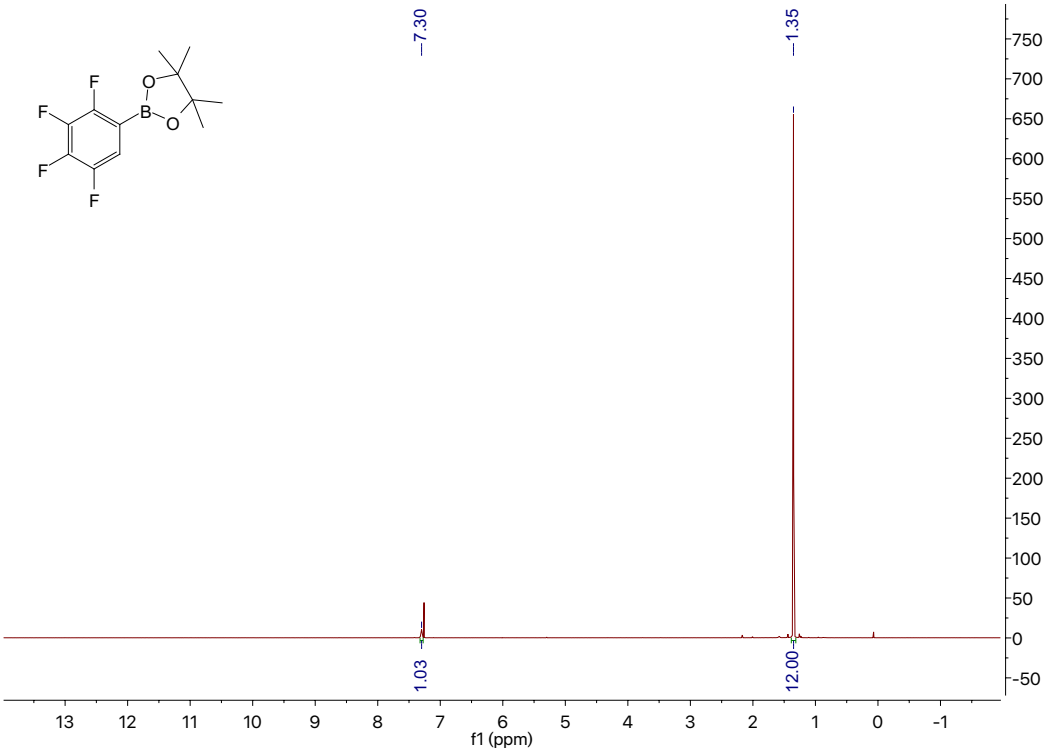
^{13}C (176 MHz, $CDCl_3$) — **68b**



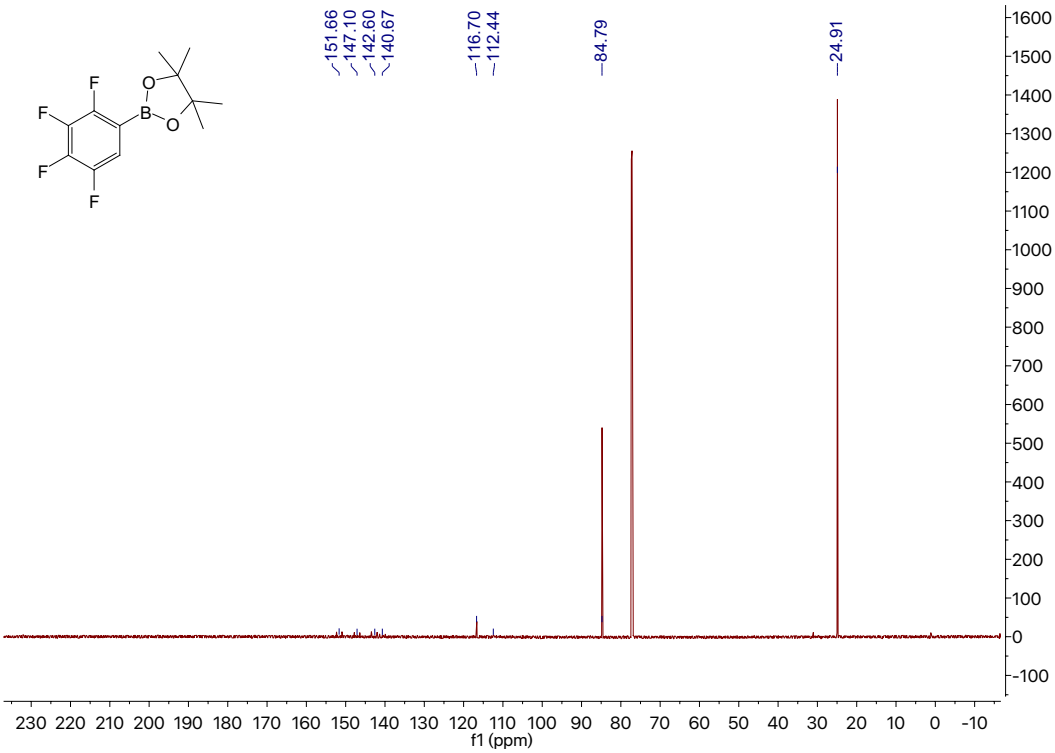
^{19}F (376 MHz, $CDCl_3$) — **68b**



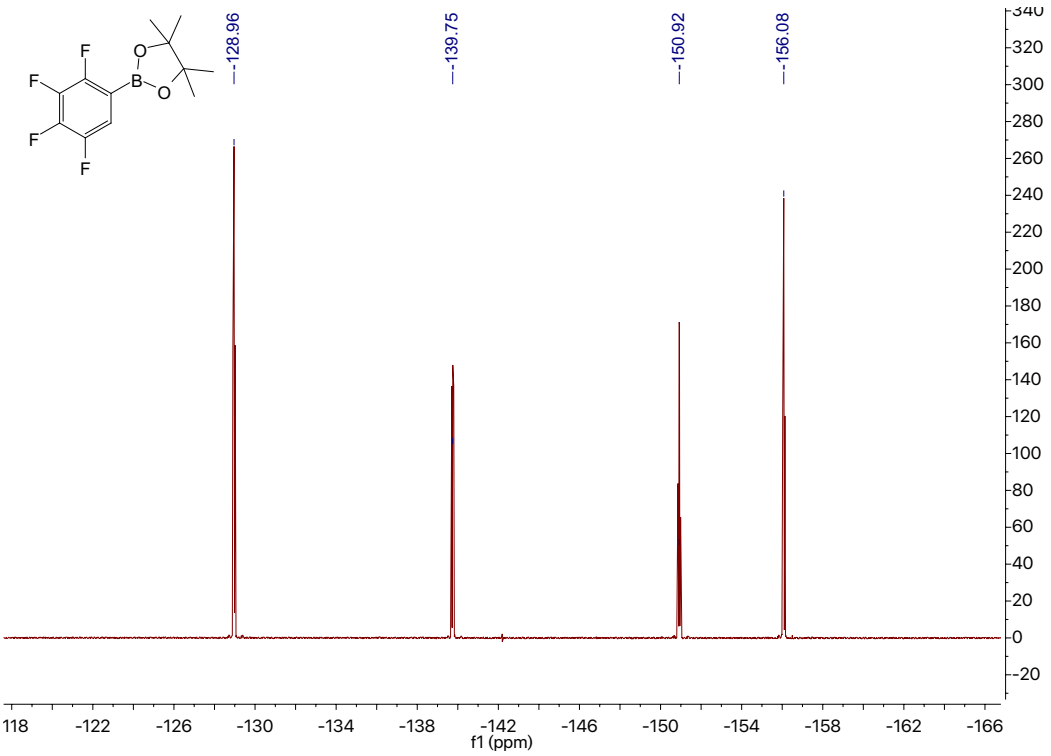
^{1}H (700 MHz, $CDCl_3$) — **69a**



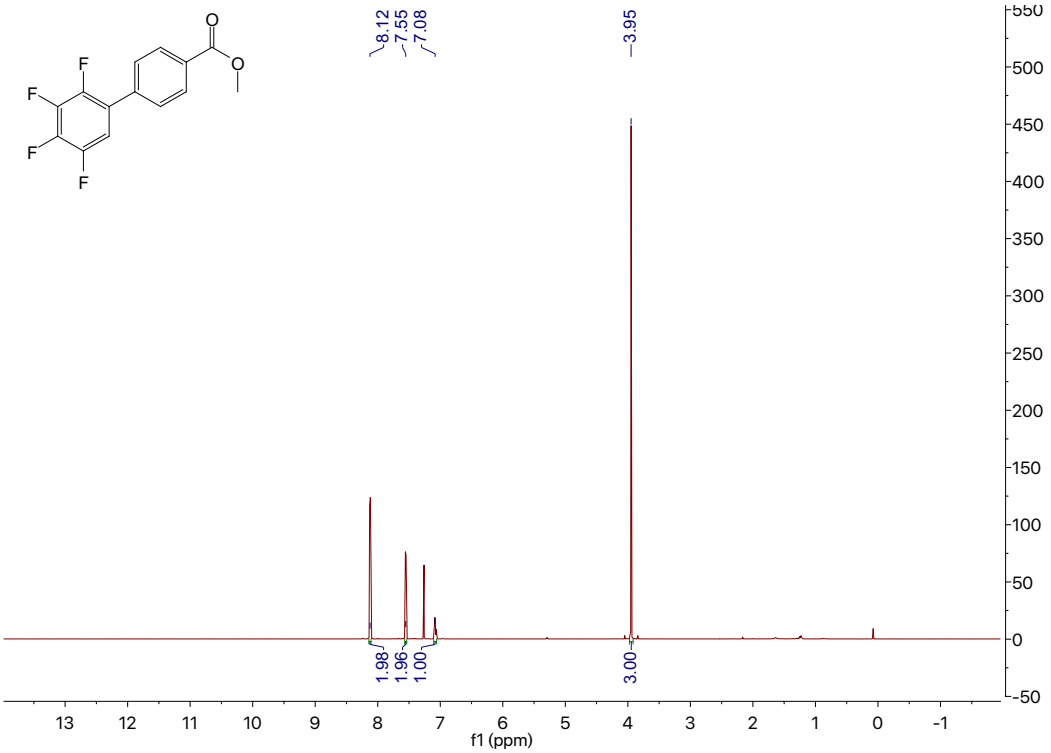
^{13}C (176 MHz, $CDCl_3$) — **69a**



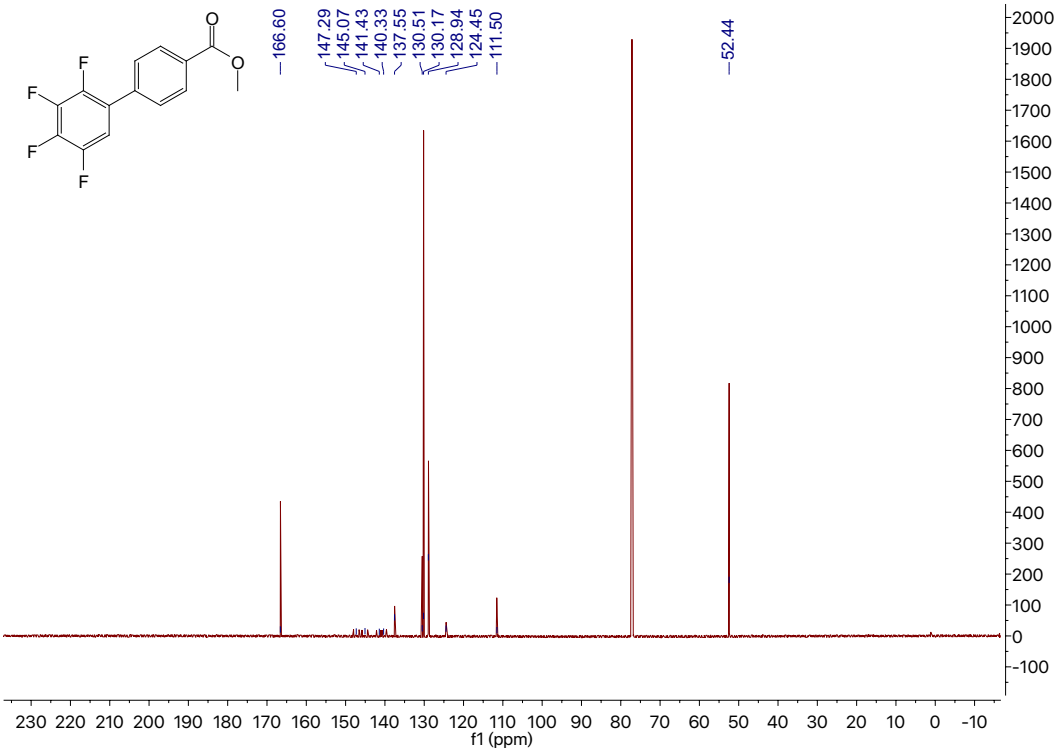
^{19}F (376 MHz, $CDCl_3$) — **69a**



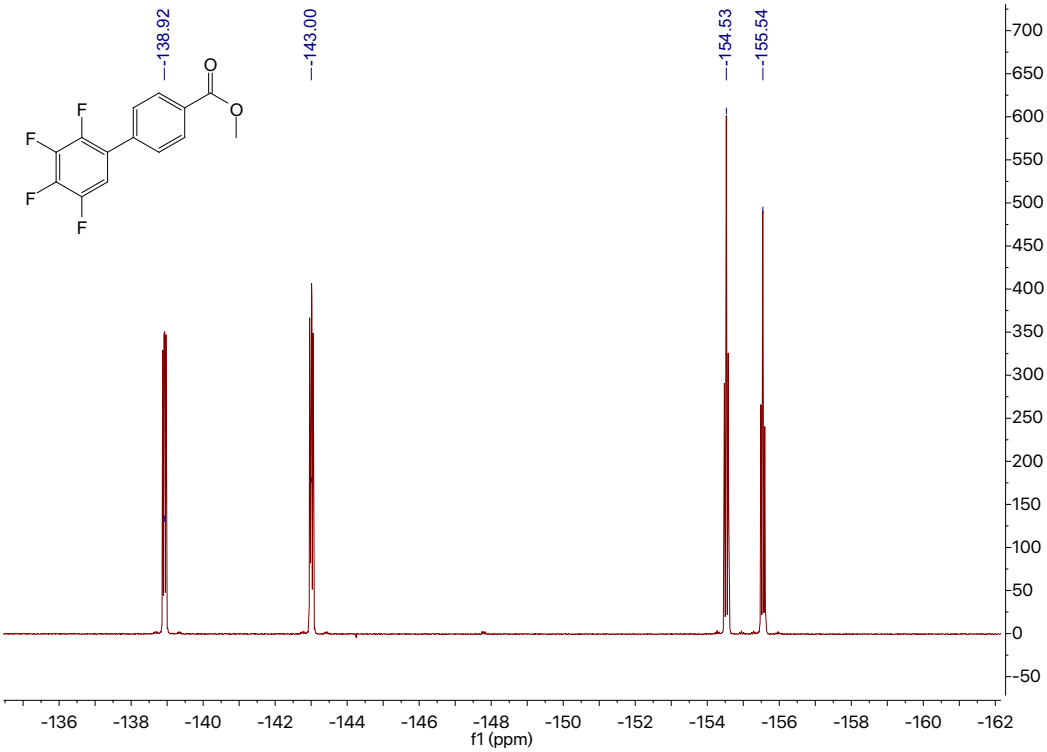
^{1}H (700 MHz, $CDCl_3$) — **69b**



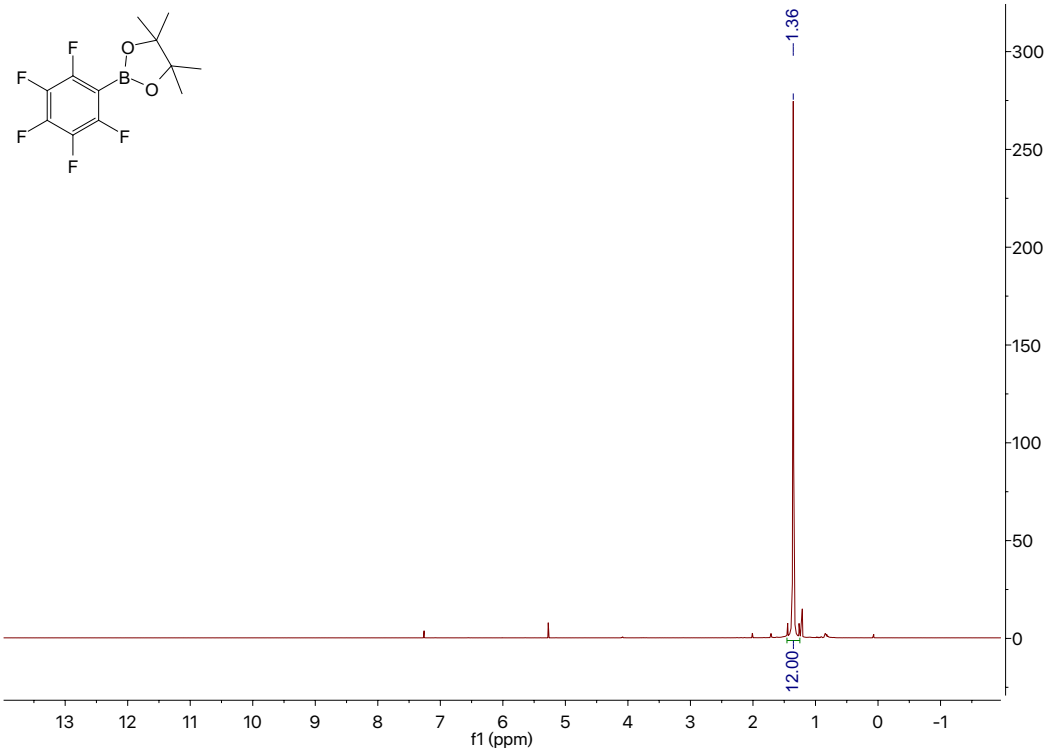
^{13}C (176 MHz, $CDCl_3$) — **69b**



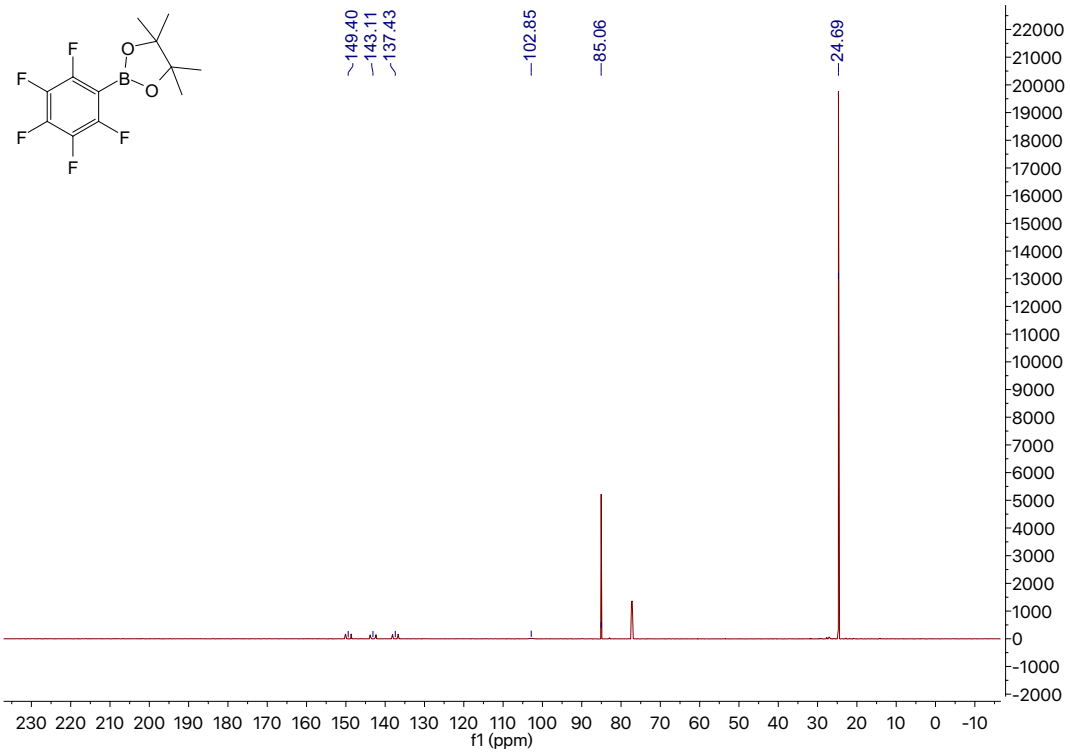
^{19}F (376 MHz, $CDCl_3$) — **69b**



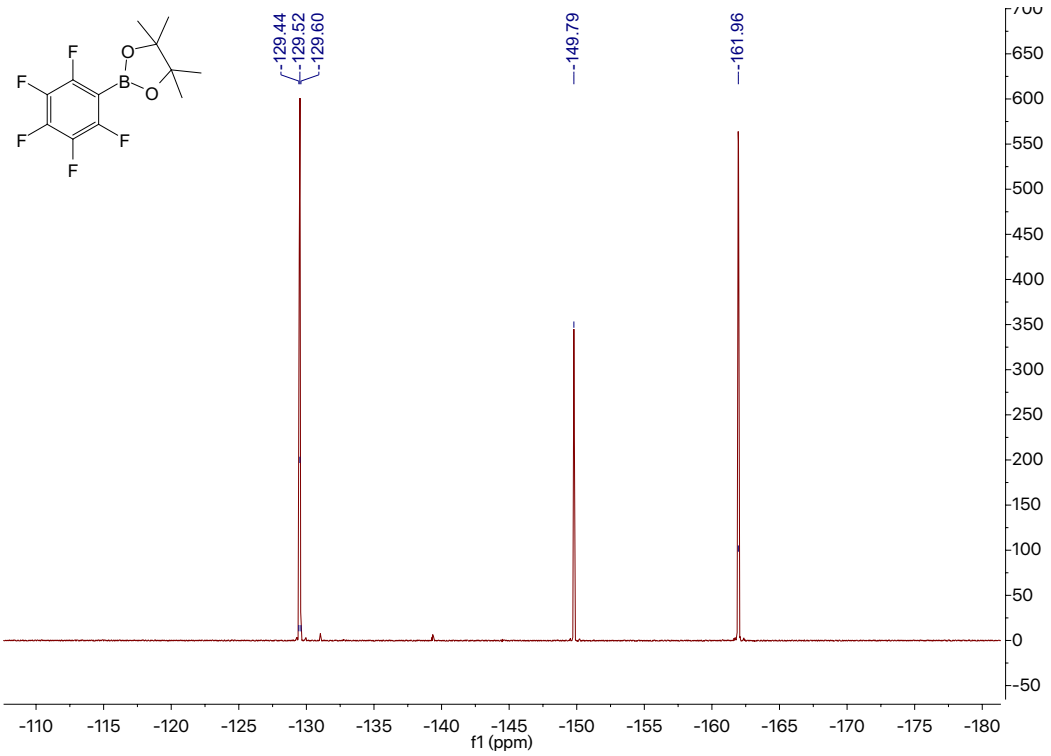
^{1}H (700 MHz, $CDCl_3$) — **70a**



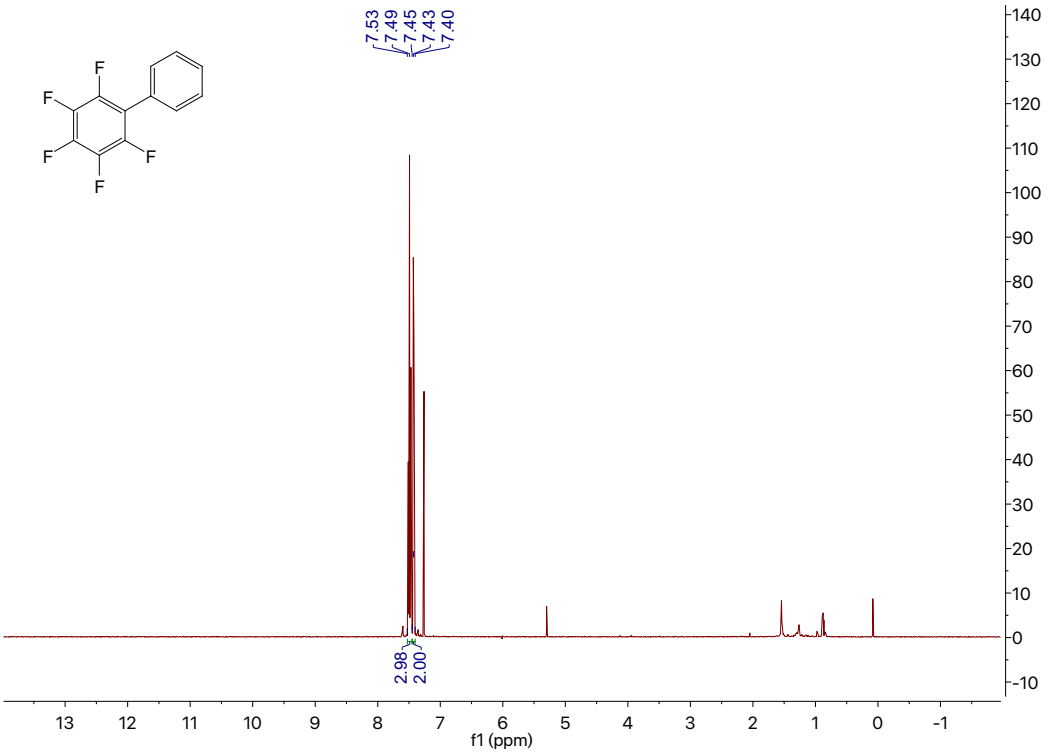
^{13}C (176 MHz, $CDCl_3$) — **70a**



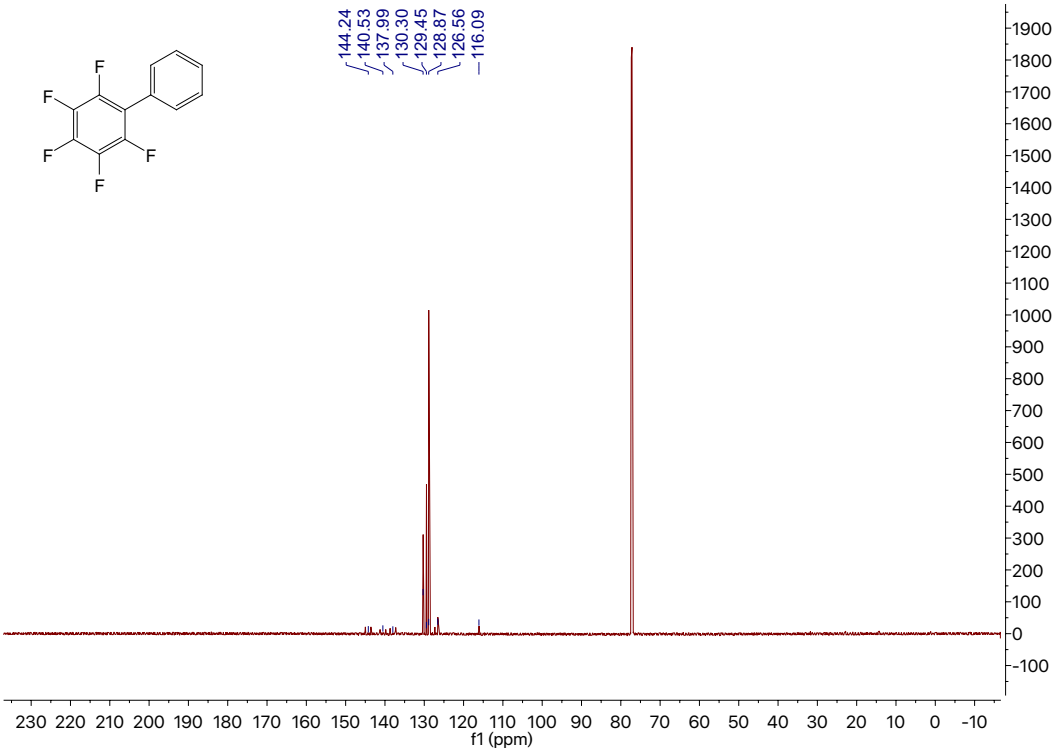
^{19}F (376 MHz, $CDCl_3$) — **70a**



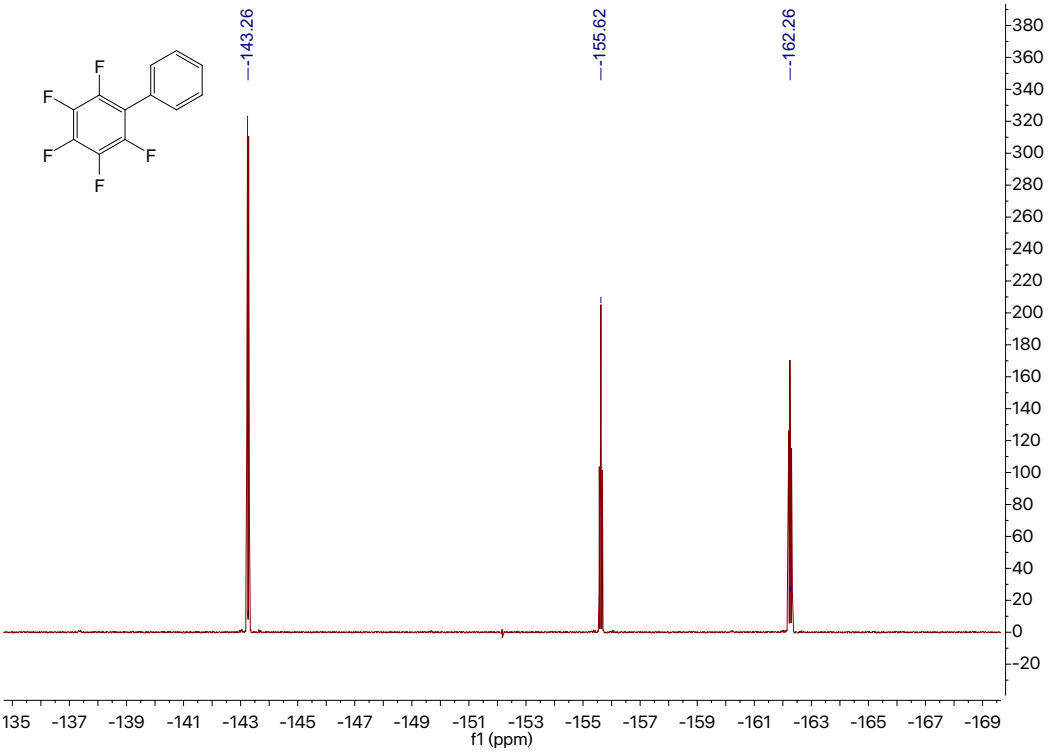
^{1}H (700 MHz, $CDCl_3$) — **70b**



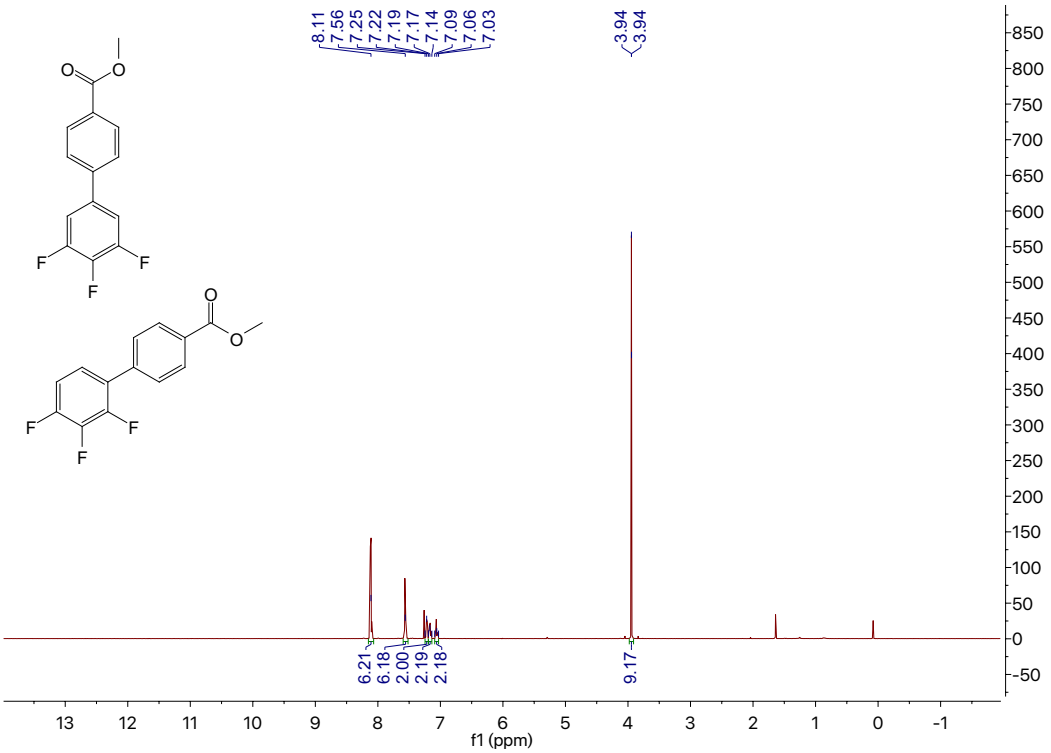
^{13}C (176 MHz, $CDCl_3$) — **70b**



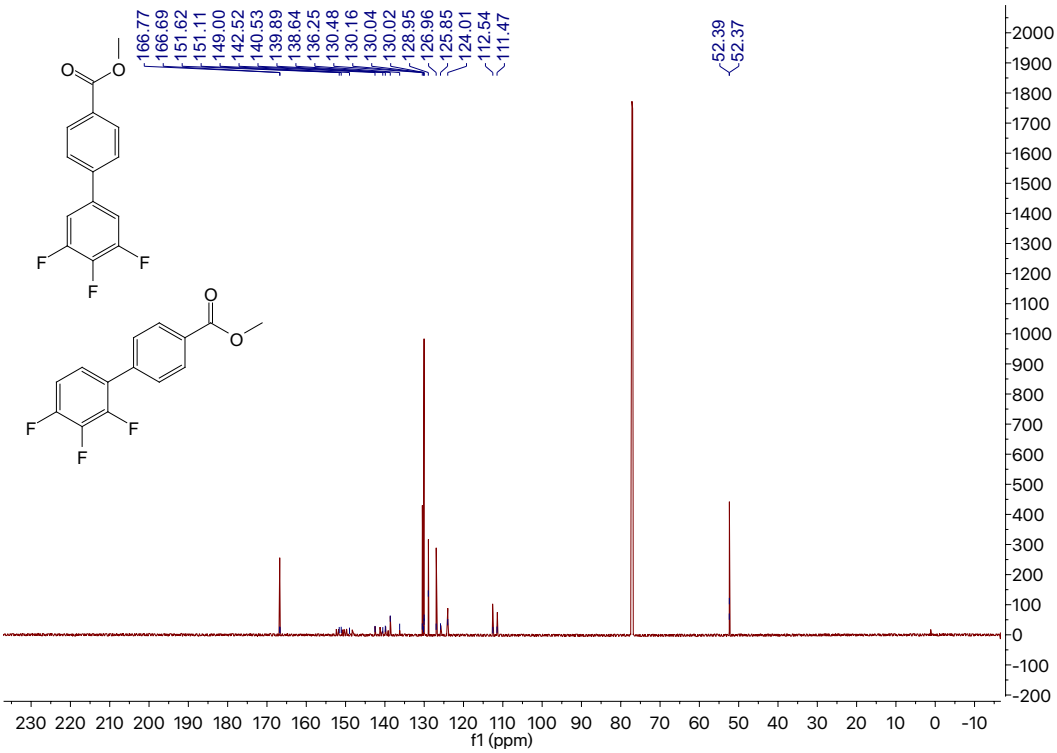
^{19}F (376 MHz, $CDCl_3$) — **70b**



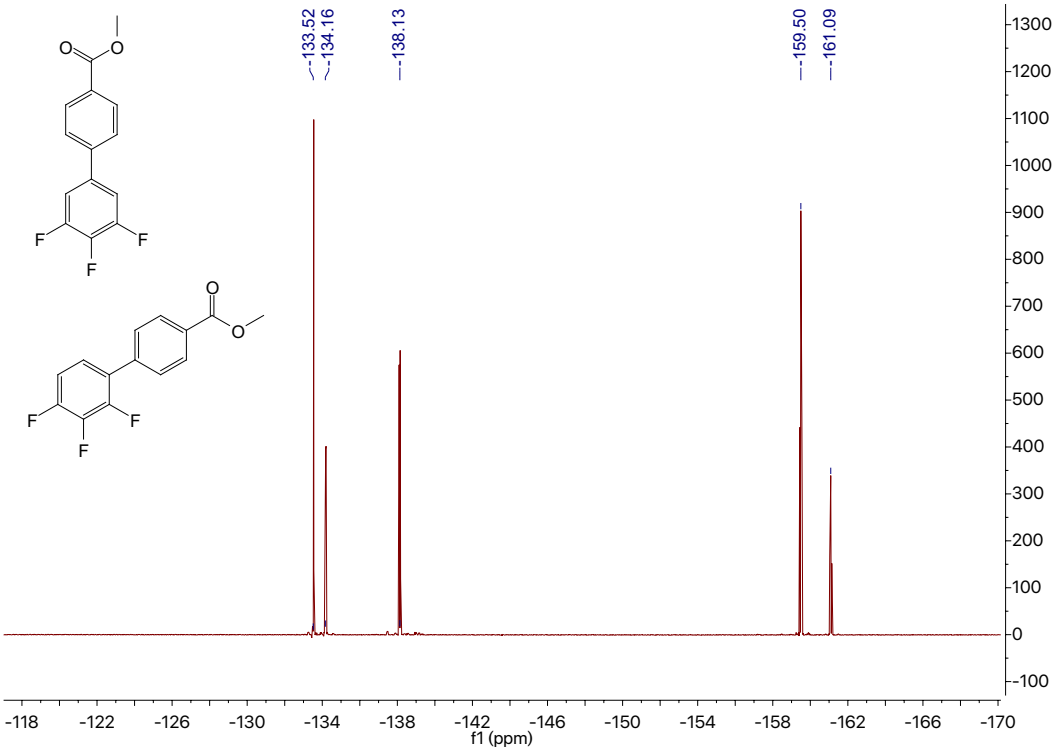
^{1}H (700 MHz, $CDCl_3$) — mixture of **71d** and **71e** (32 : 68)



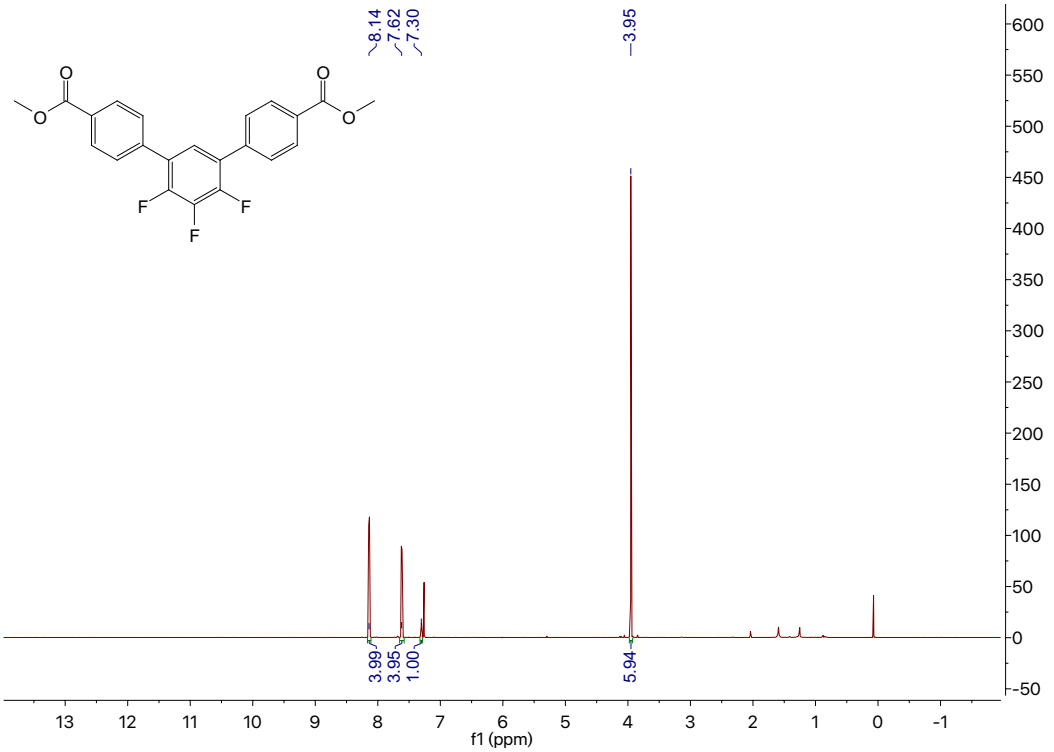
^{13}C (176 MHz, $CDCl_3$) — mixture of **71d** and **71e** (32 : 68)



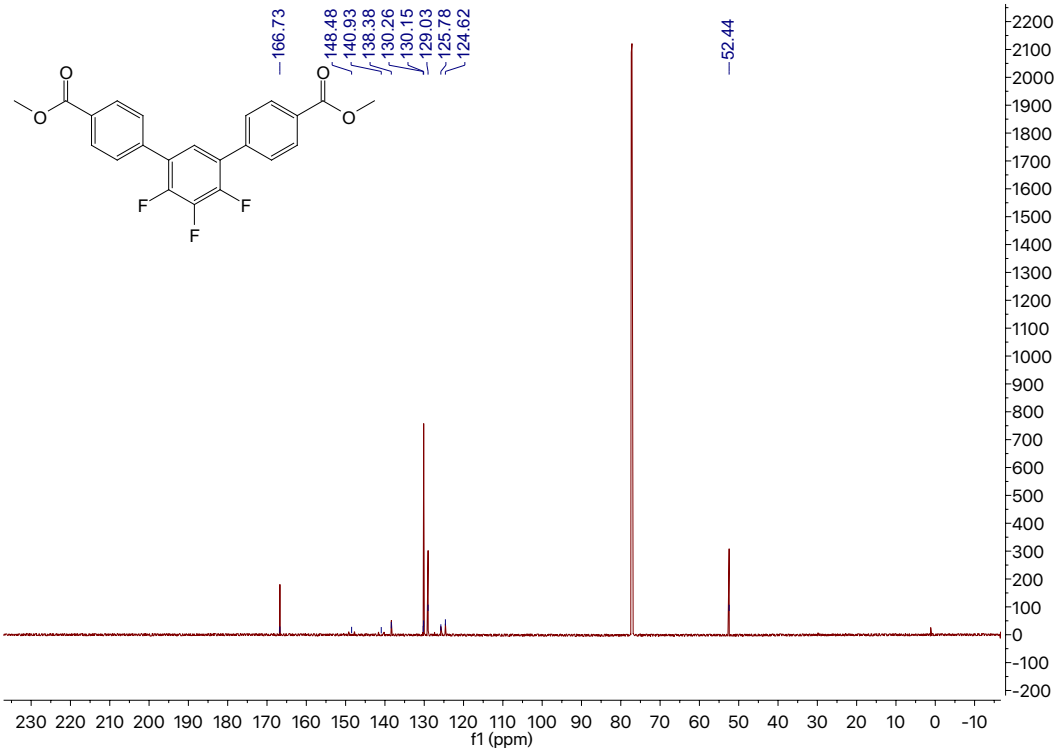
^{19}F (376 MHz, $CDCl_3$) — mixture of **71d** and **71e** (32 : 68)



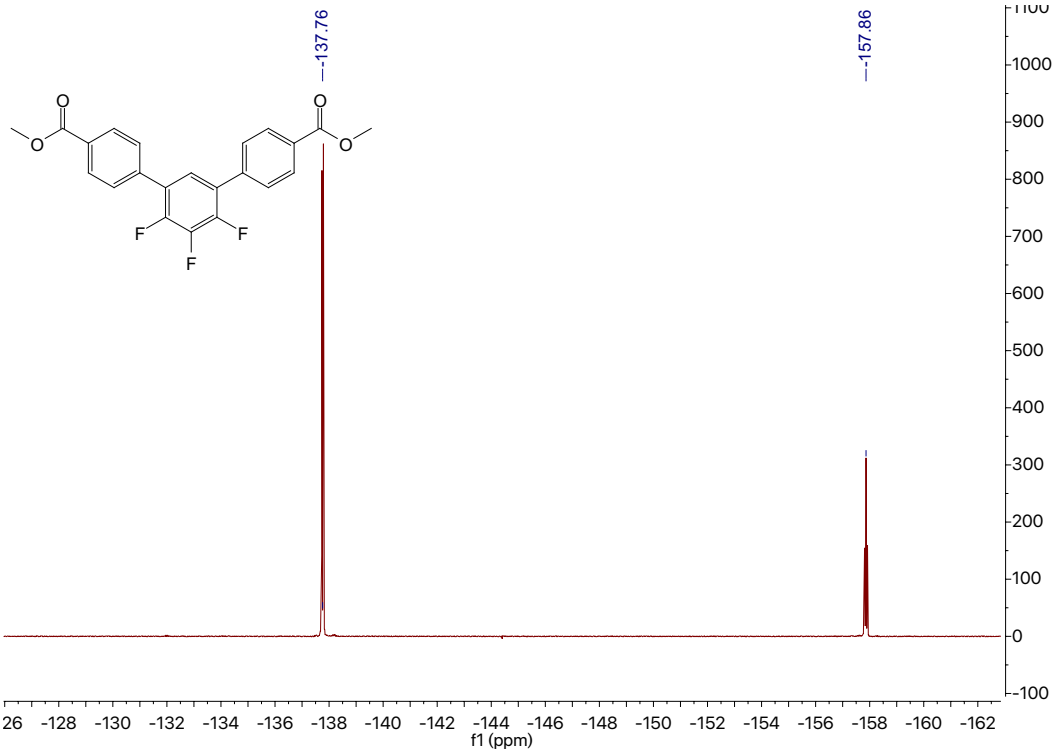
^{1}H (700 MHz, $CDCl_3$) — **71f**



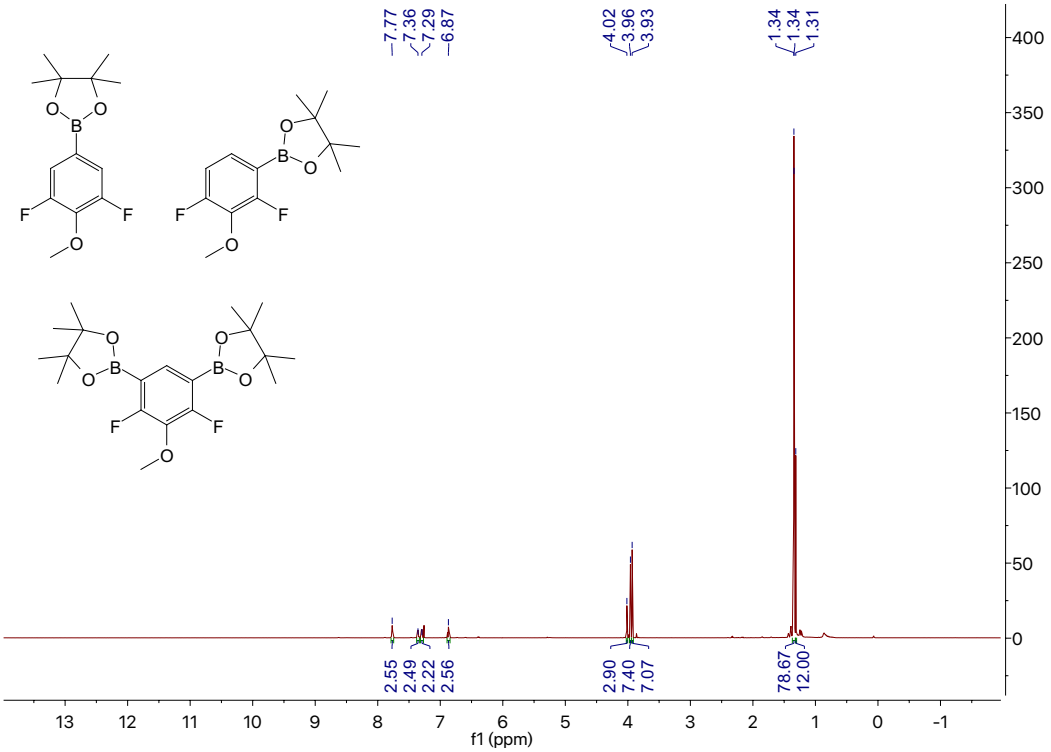
^{13}C (176 MHz, $CDCl_3$) — **71f**



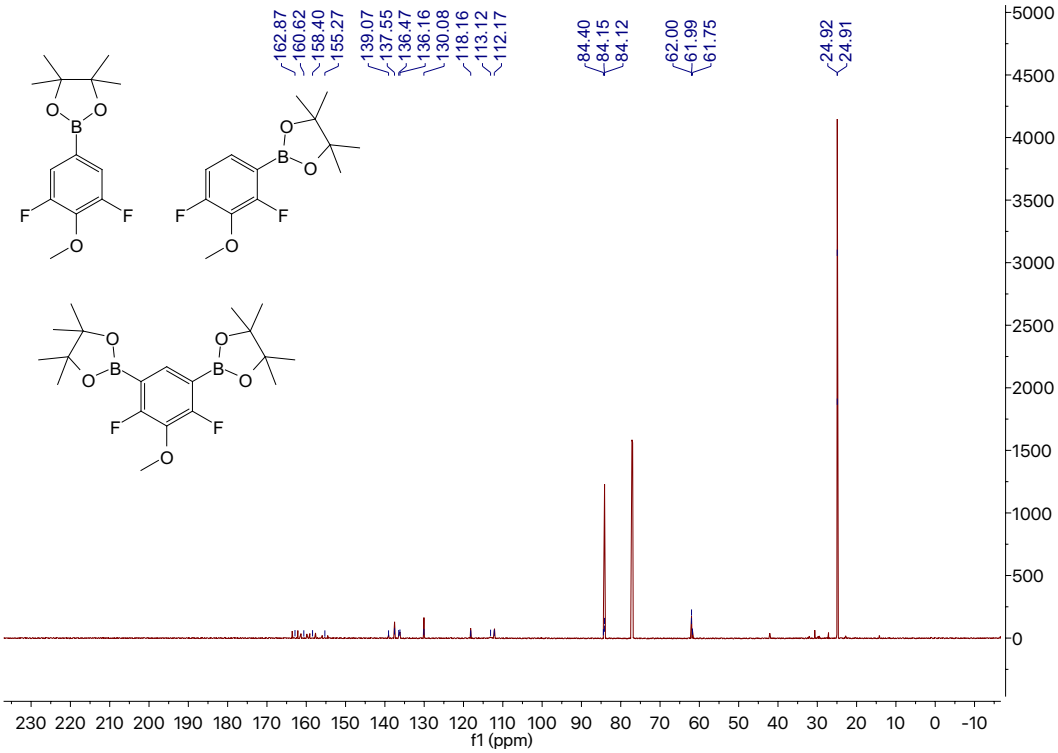
^{19}F (376 MHz, $CDCl_3$) — **71f**



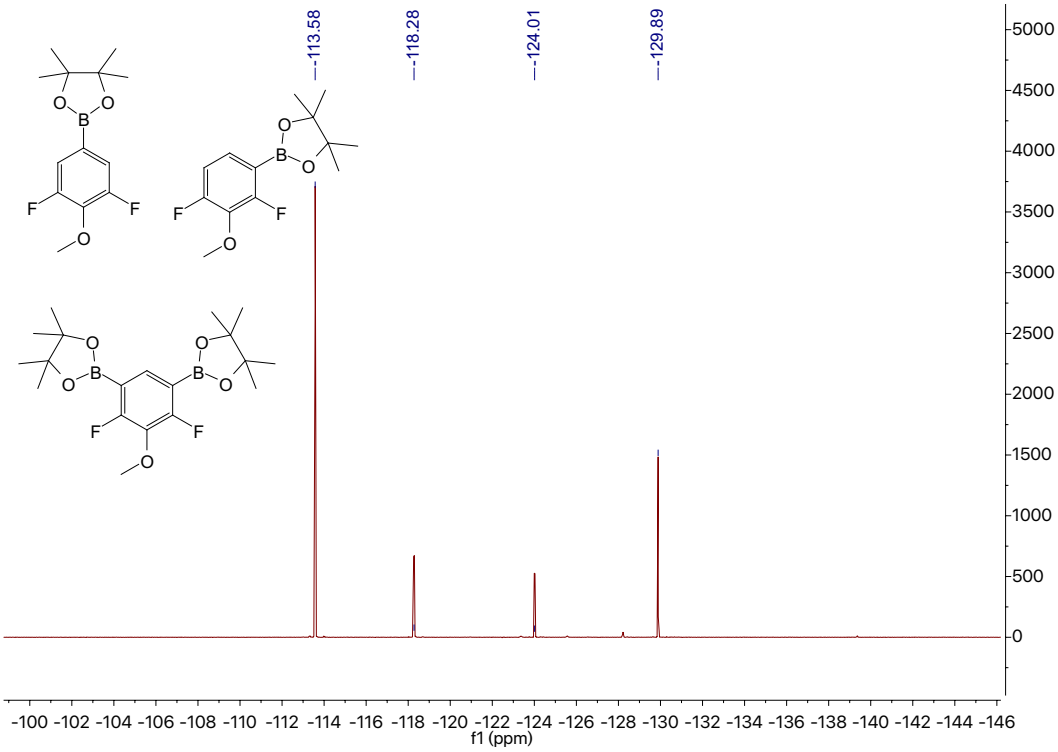
^{1}H (700 MHz, $CDCl_3$) — mixture of **73a**, **73b** and **73c** (34 : 54 : 2)



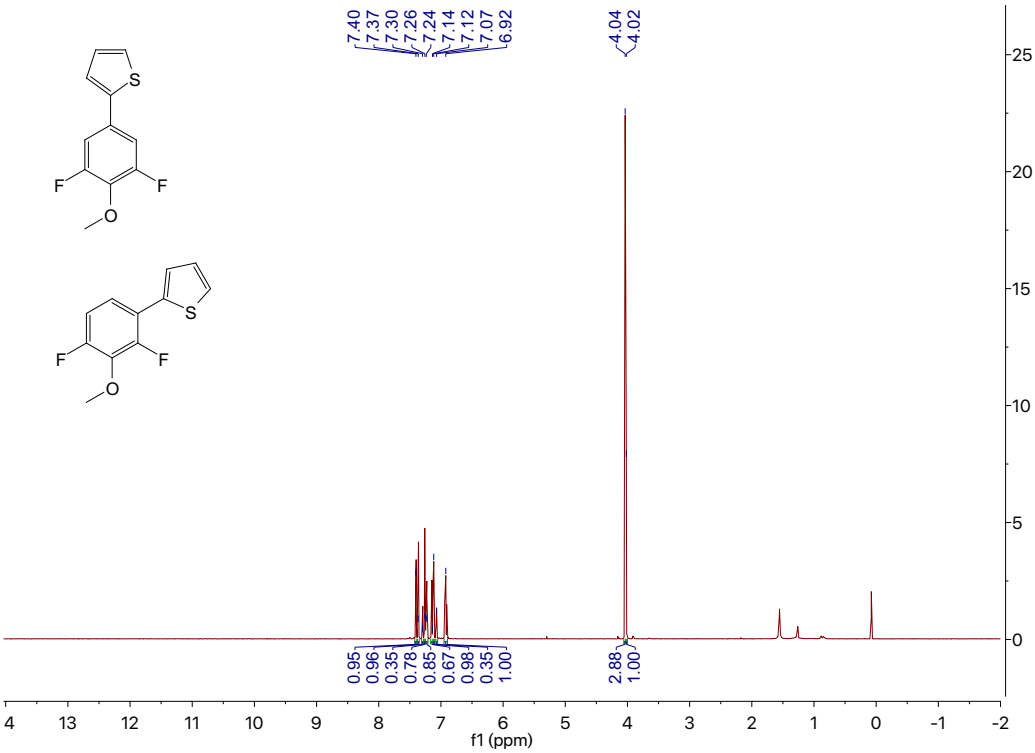
^{13}C (176 MHz, $CDCl_3$) — mixture of **73a**, **73b** and **73c** (34 : 54 : 2)



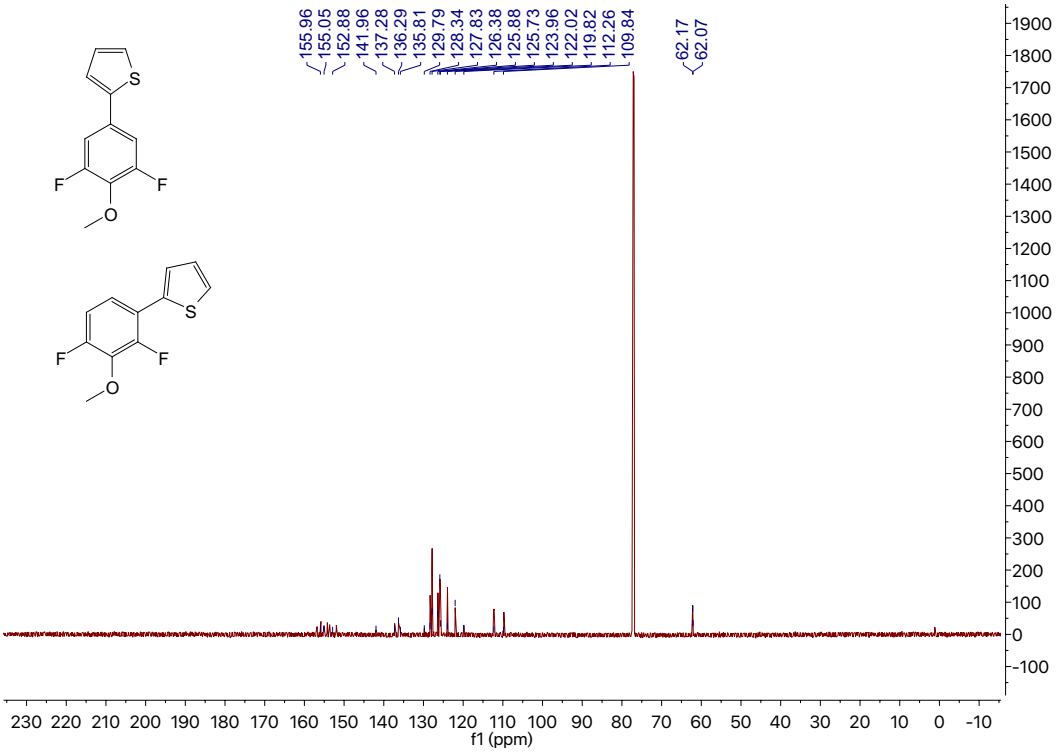
^{19}F (376 MHz, $CDCl_3$) — mixture of **73a**, **73b** and **73c** (34 : 54 : 2)



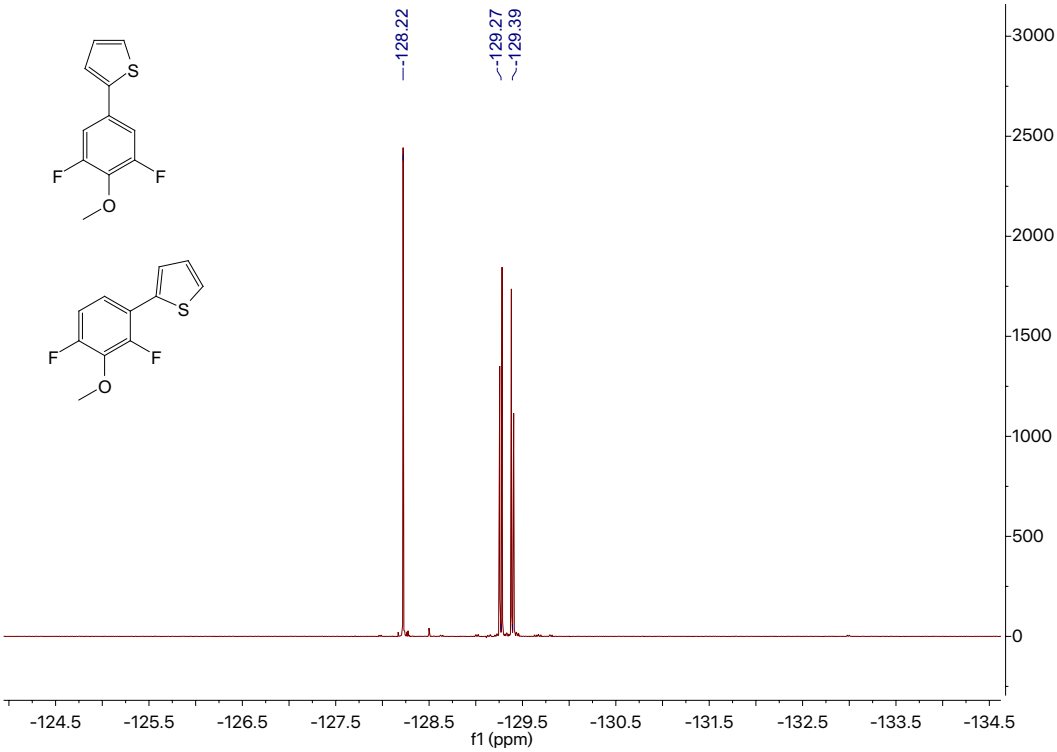
^{1}H (599 MHz, $CDCl_3$) — mixture of **73d** and **73e** (27 : 73)



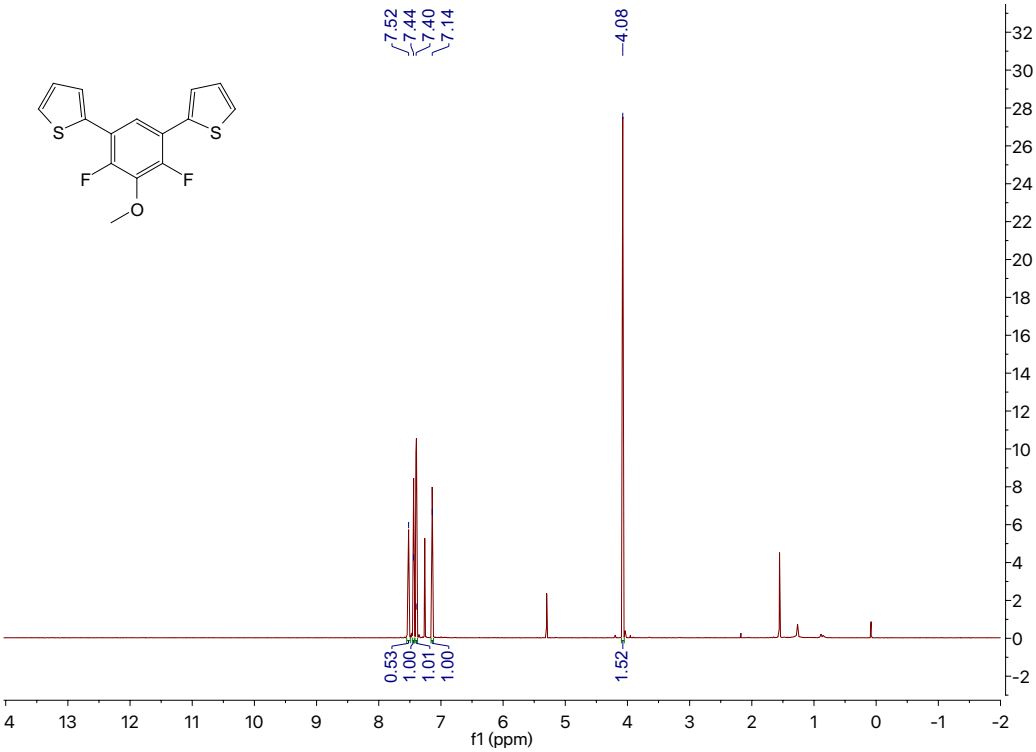
^{13}C (151 MHz, $CDCl_3$) — mixture of **73d** and **73e** (27 : 73)



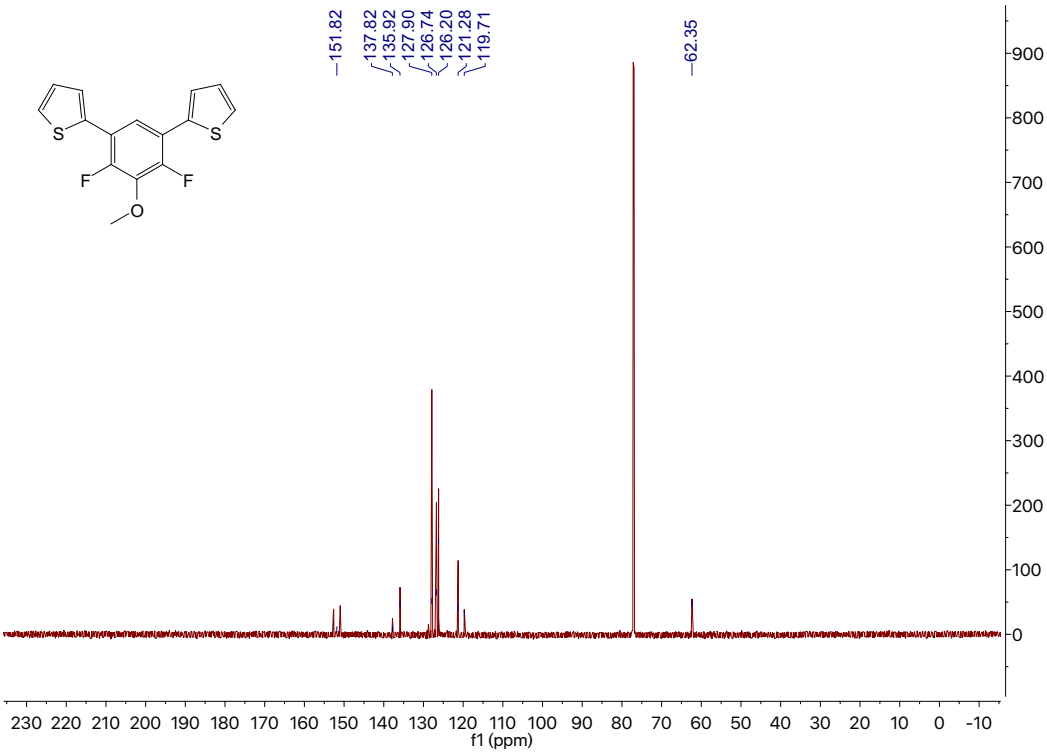
^{19}F (376 MHz, $CDCl_3$) — mixture of **73d** and **73e** (27 : 73)



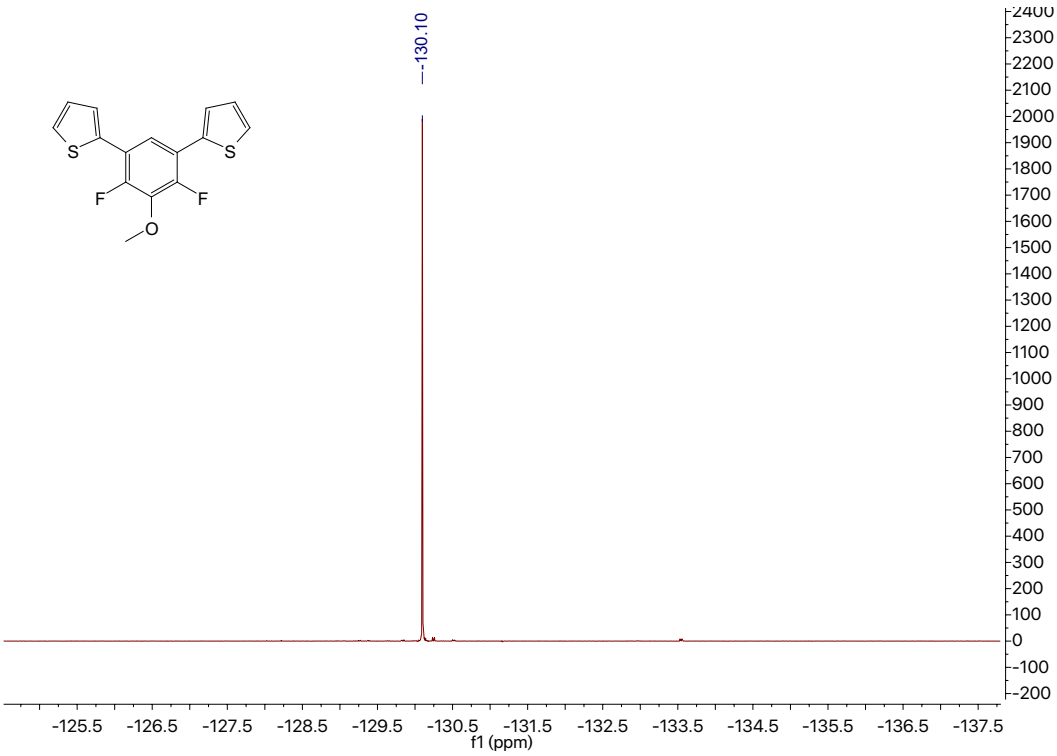
^{1}H (599 MHz, $CDCl_3$) — **73f**



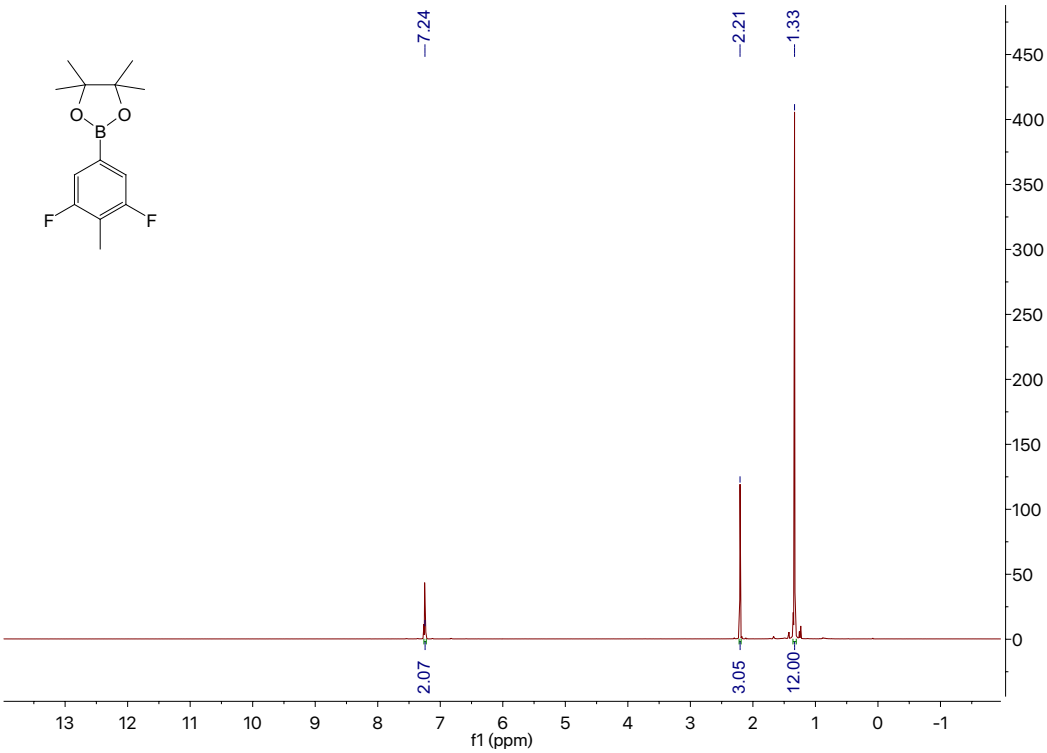
^{13}C (151 MHz, $CDCl_3$) — **73f**



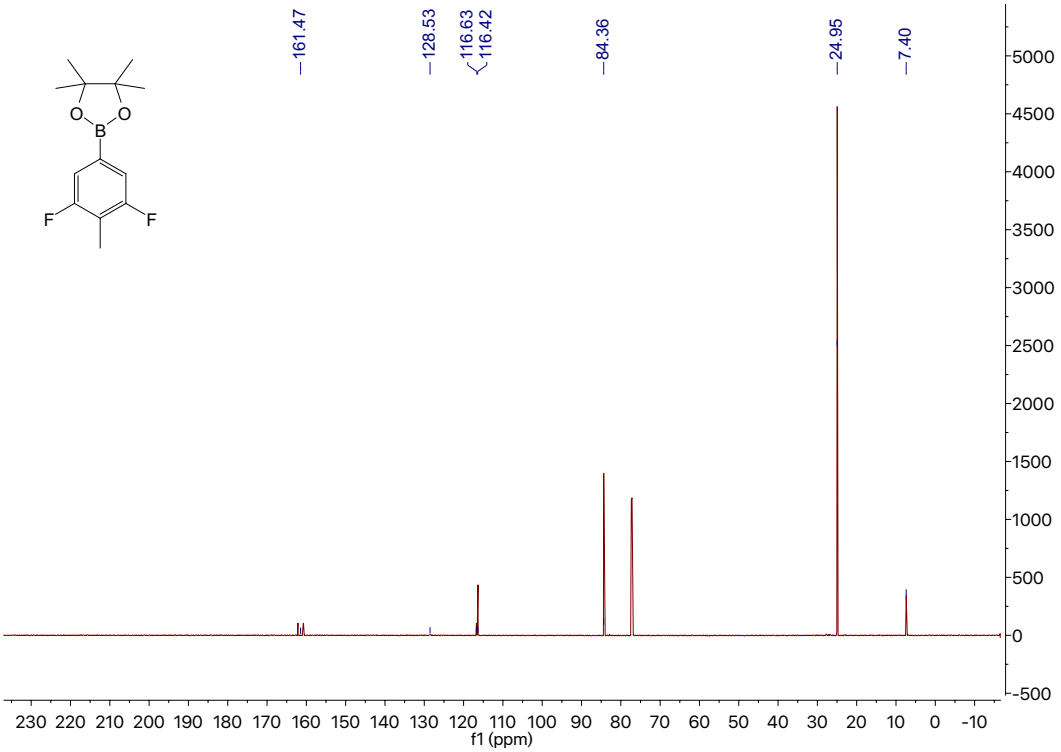
^{19}F (376 MHz, $CDCl_3$) — **73f**



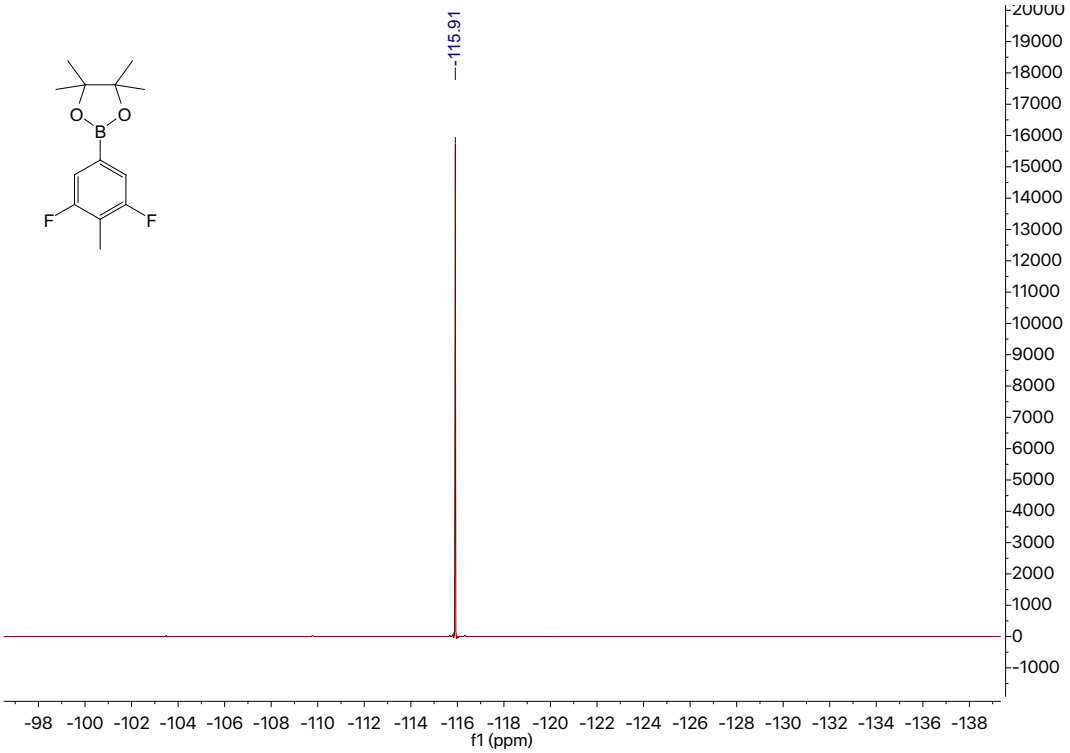
^{1}H (700 MHz, $CDCl_3$) — **74a**



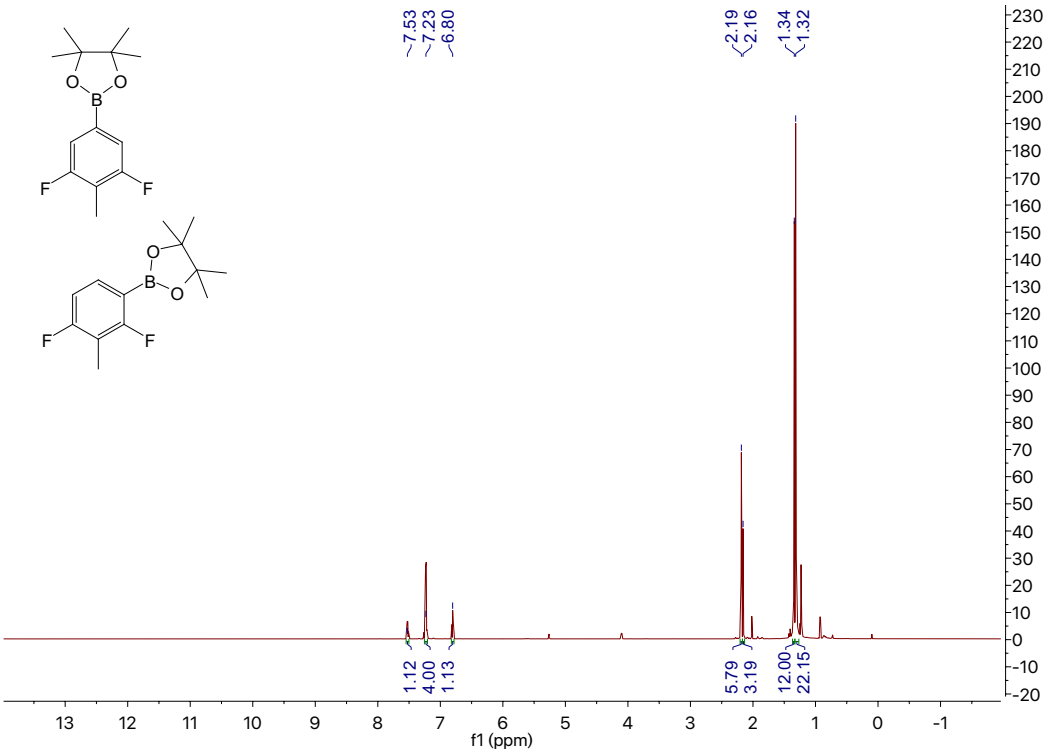
^{13}C (176 MHz, $CDCl_3$) — **74a**



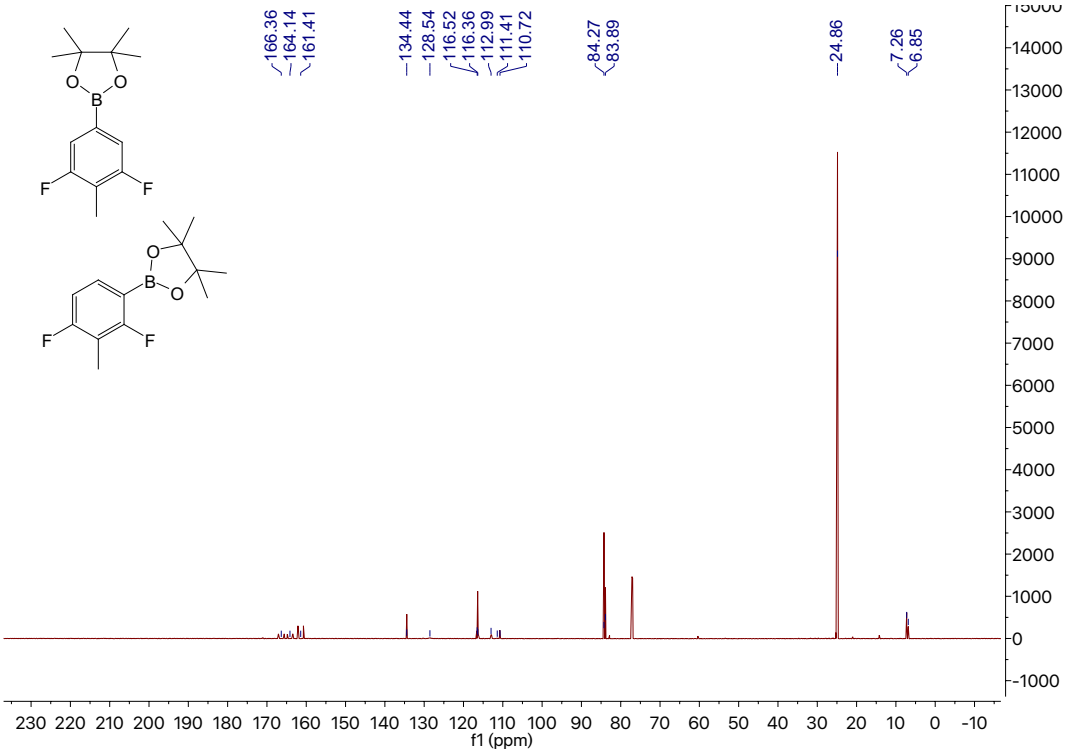
^{19}F (376 MHz, $CDCl_3$) — **74a**



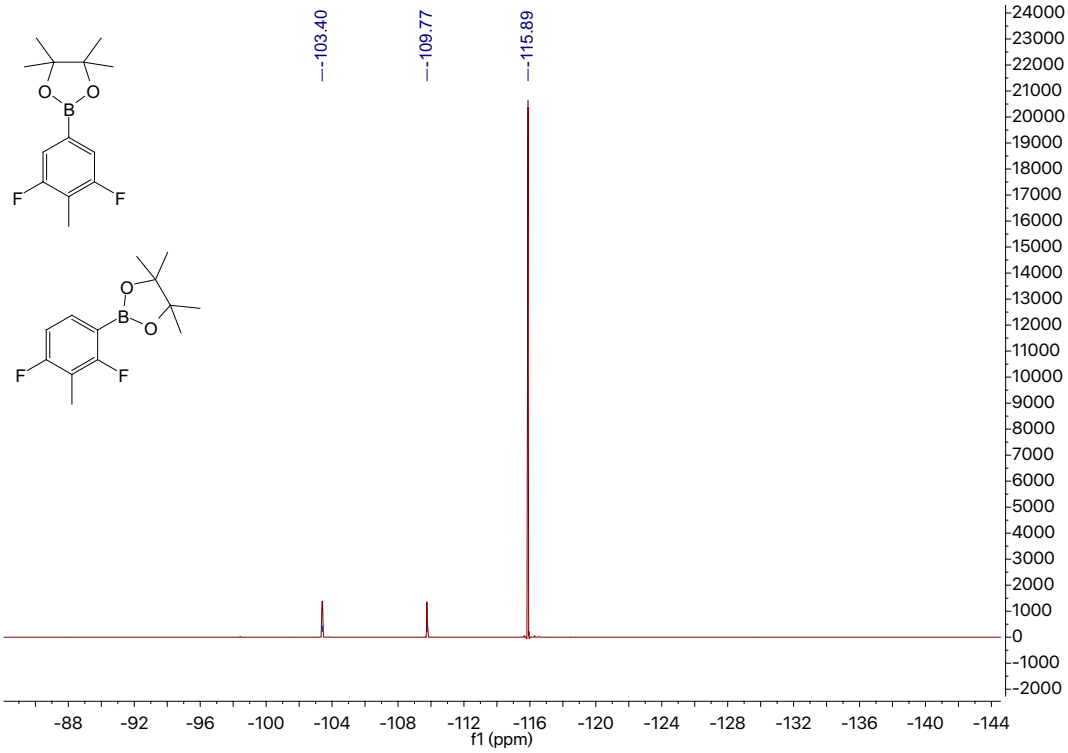
^{1}H (700 MHz, $CDCl_3$) — mixture of **74a** and **74b** (50 : 50)



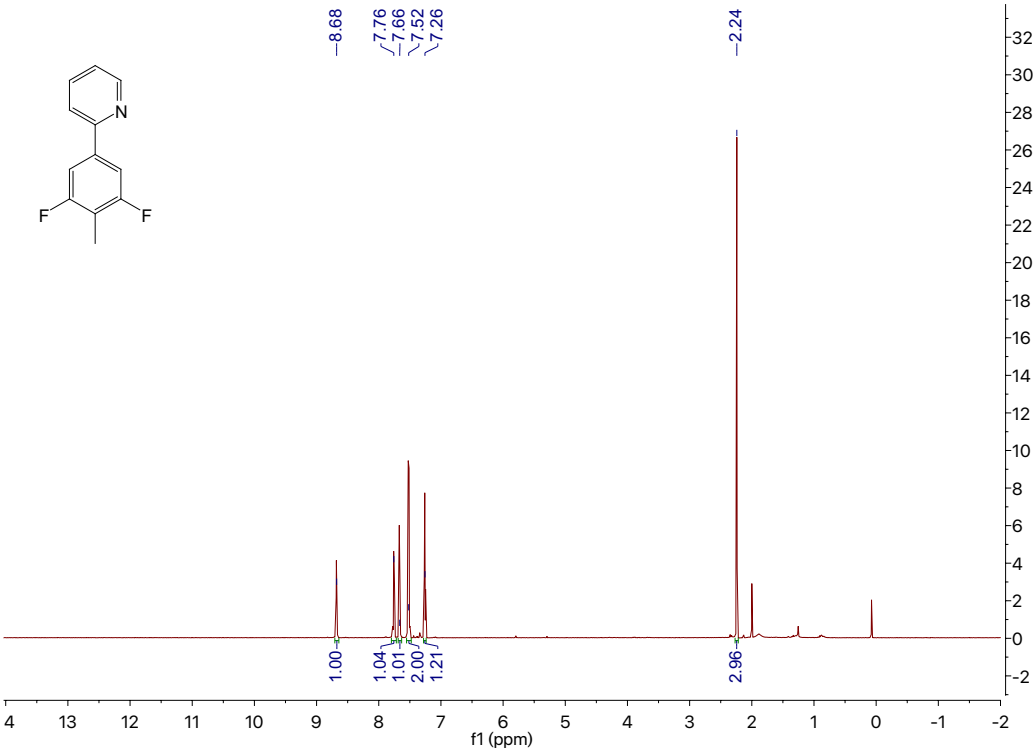
^{13}C (176 MHz, $CDCl_3$) — mixture of **74a** and **74b** (50 : 50)



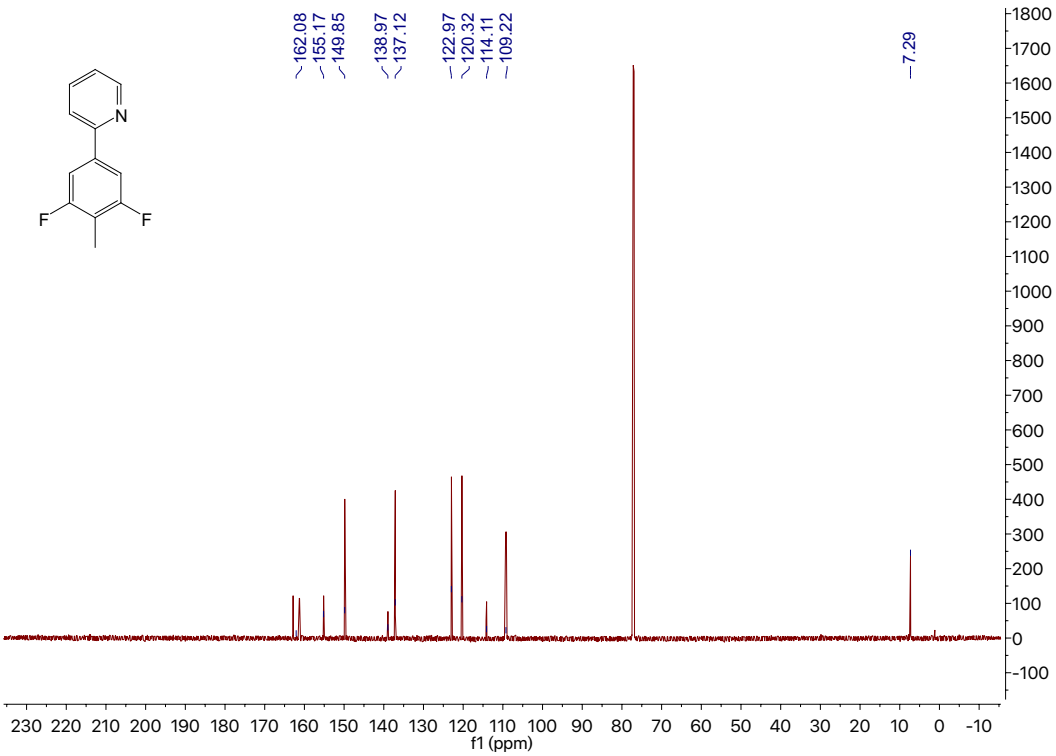
^{19}F (376 MHz, $CDCl_3$) — mixture of **74a** and **74b** (50 : 50)



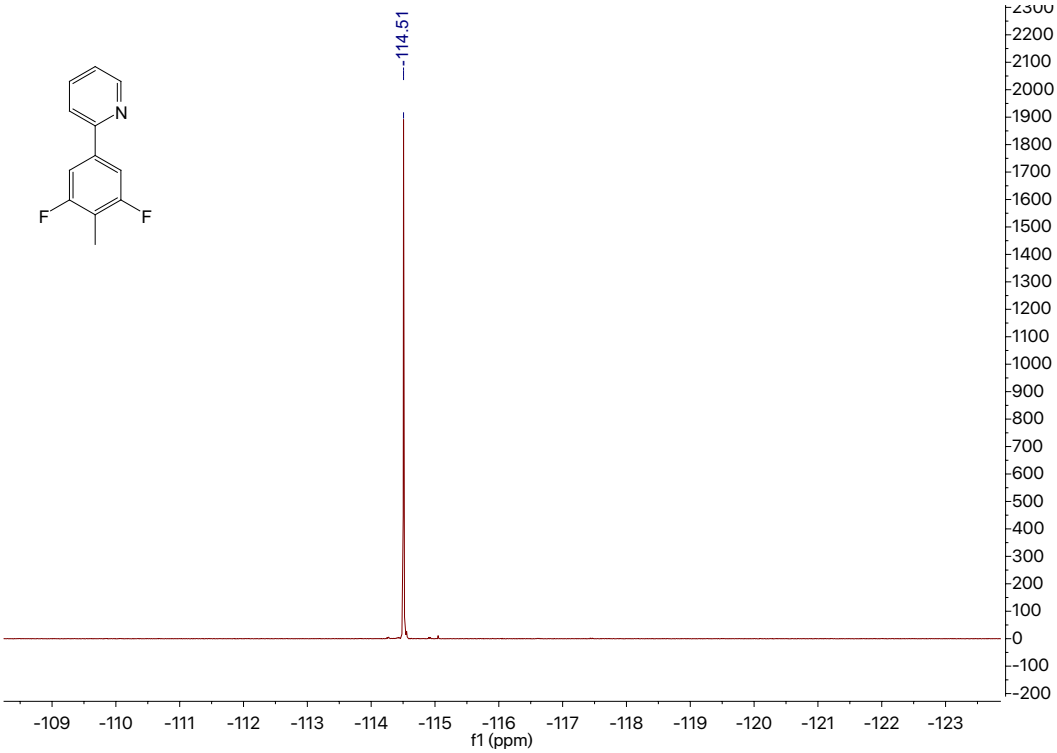
^{1}H (599 MHz, $CDCl_3$) — **74d**



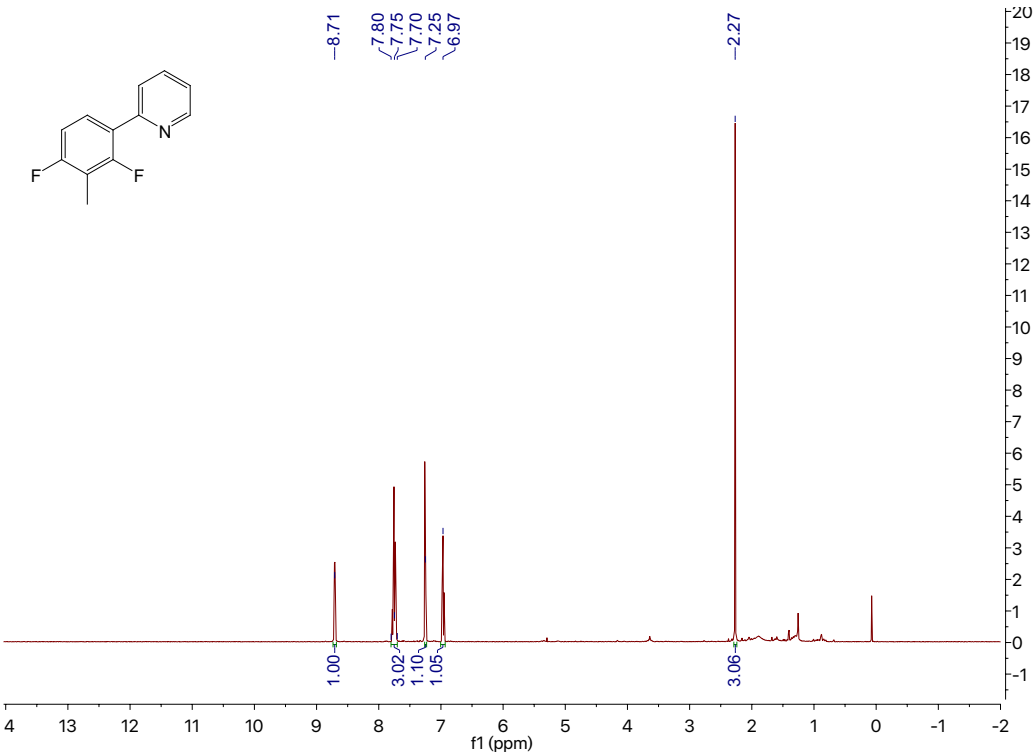
^{13}C (151 MHz, $CDCl_3$) — **74d**



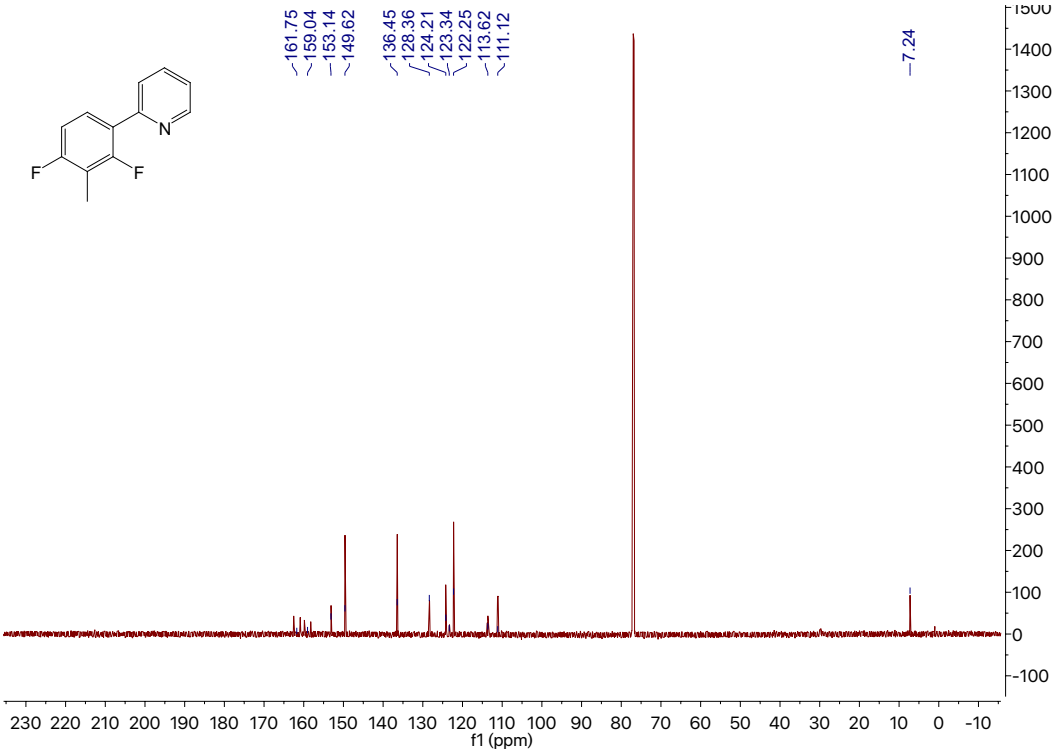
^{19}F (376 MHz, $CDCl_3$) — **74d**



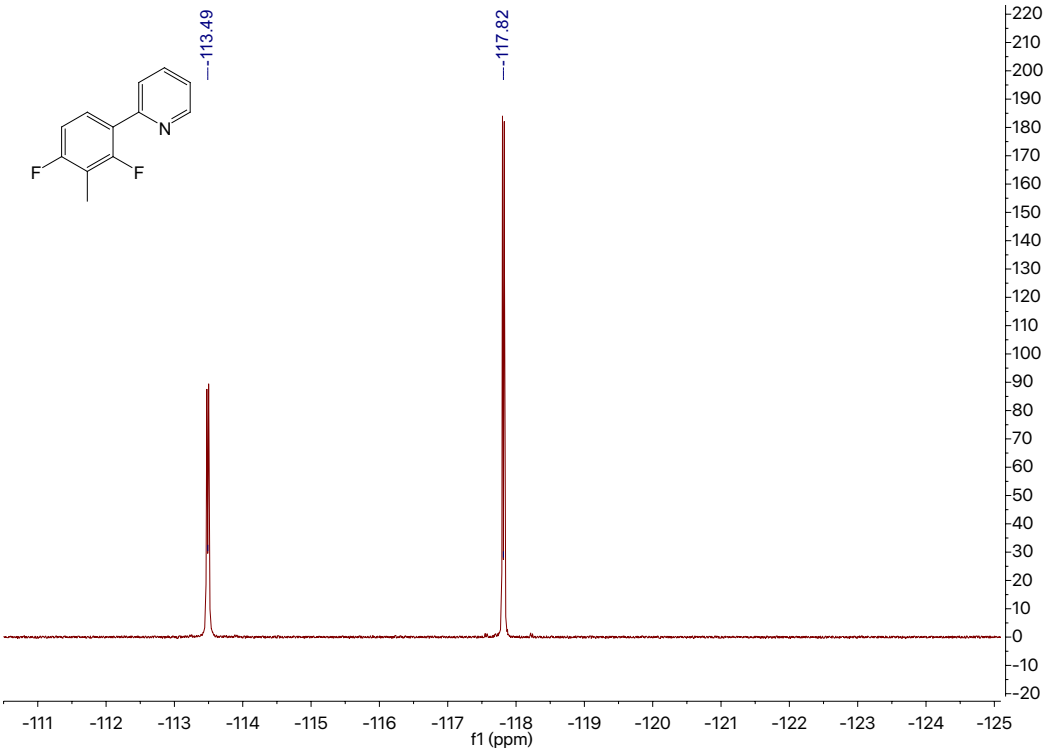
^{1}H (599 MHz, $CDCl_3$) — **74e**



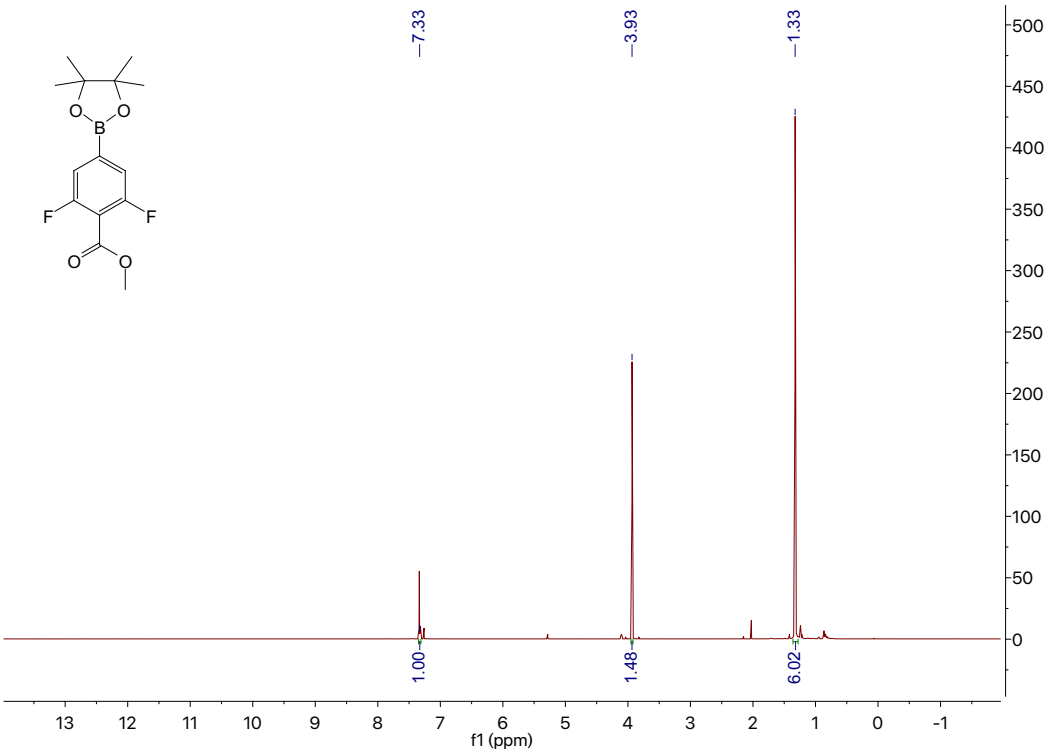
^{13}C (151 MHz, $CDCl_3$) — **74e**



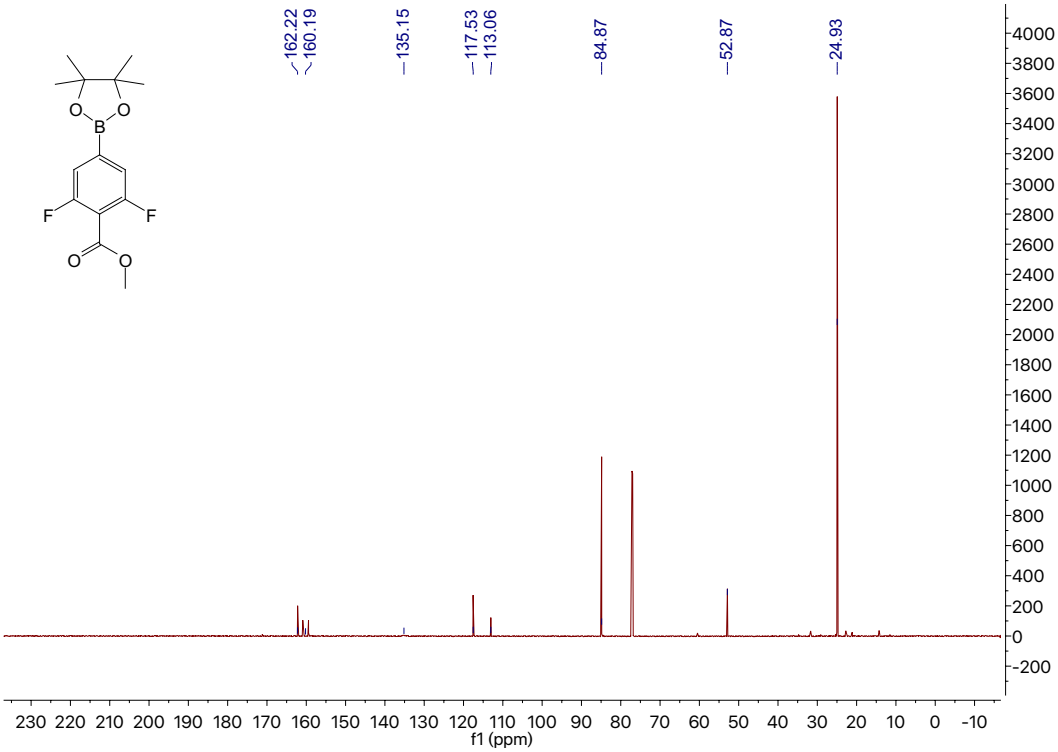
^{19}F (376 MHz, $CDCl_3$) — **74e**



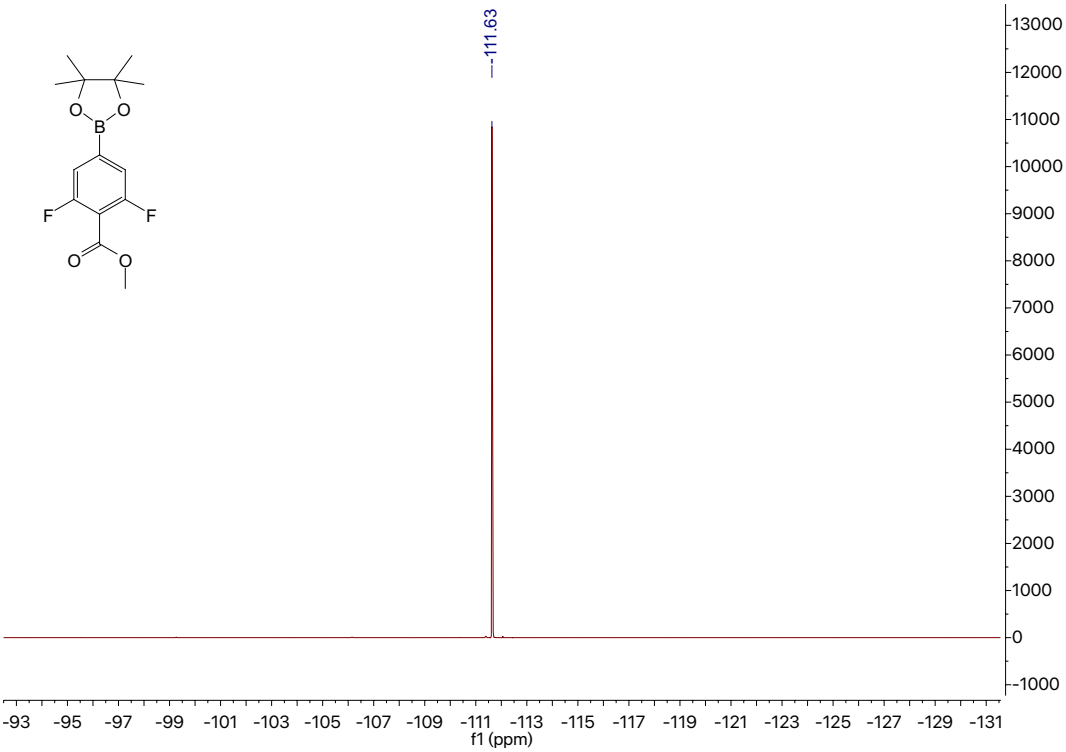
^{1}H (700 MHz, $CDCl_3$) — **75a**



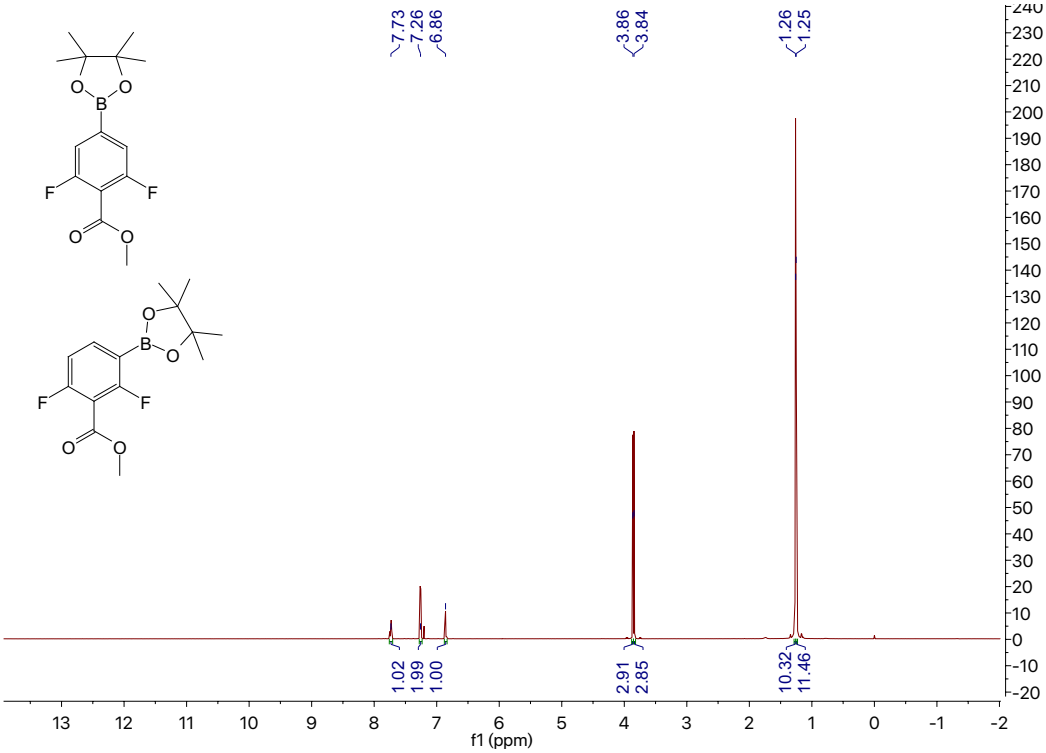
^{13}C (176 MHz, $CDCl_3$) — **75a**



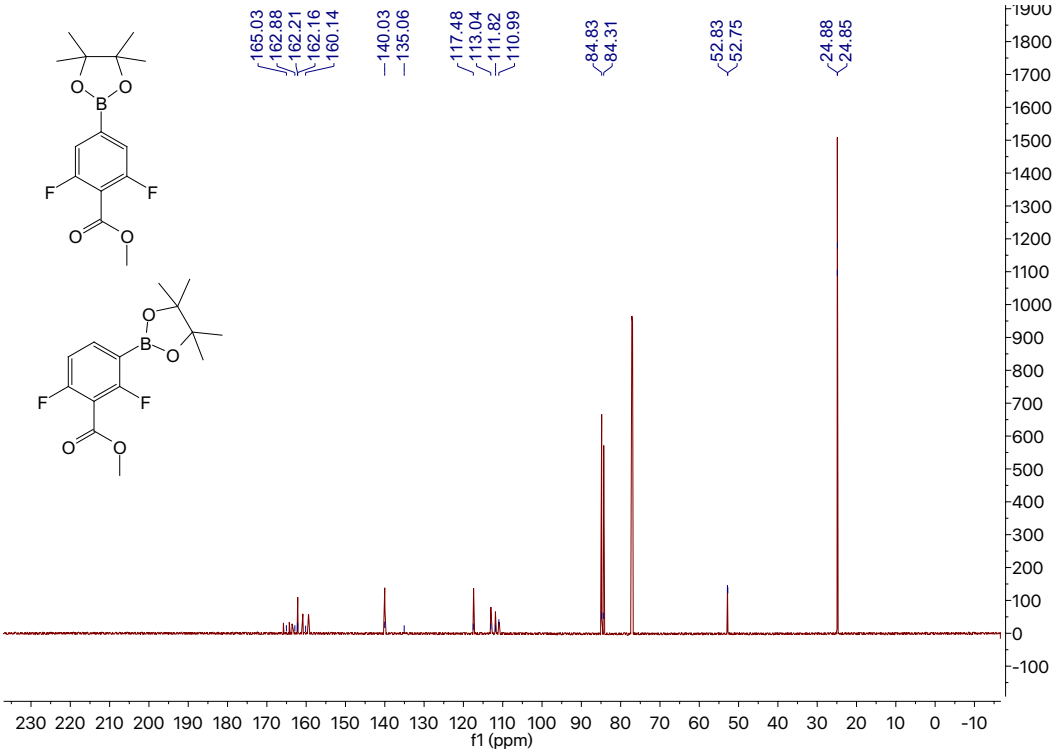
^{19}F (376 MHz, $CDCl_3$) — **75a**



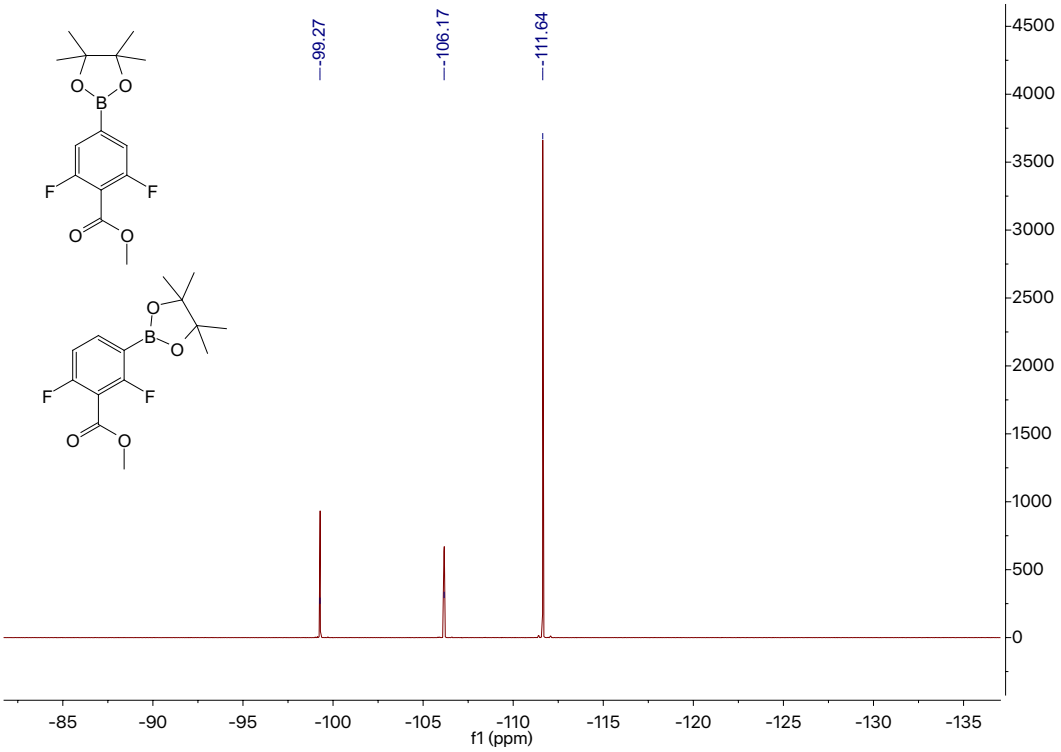
^{1}H (700 MHz, $CDCl_3$) — mixture of **75a** and **75b** (52 : 48)



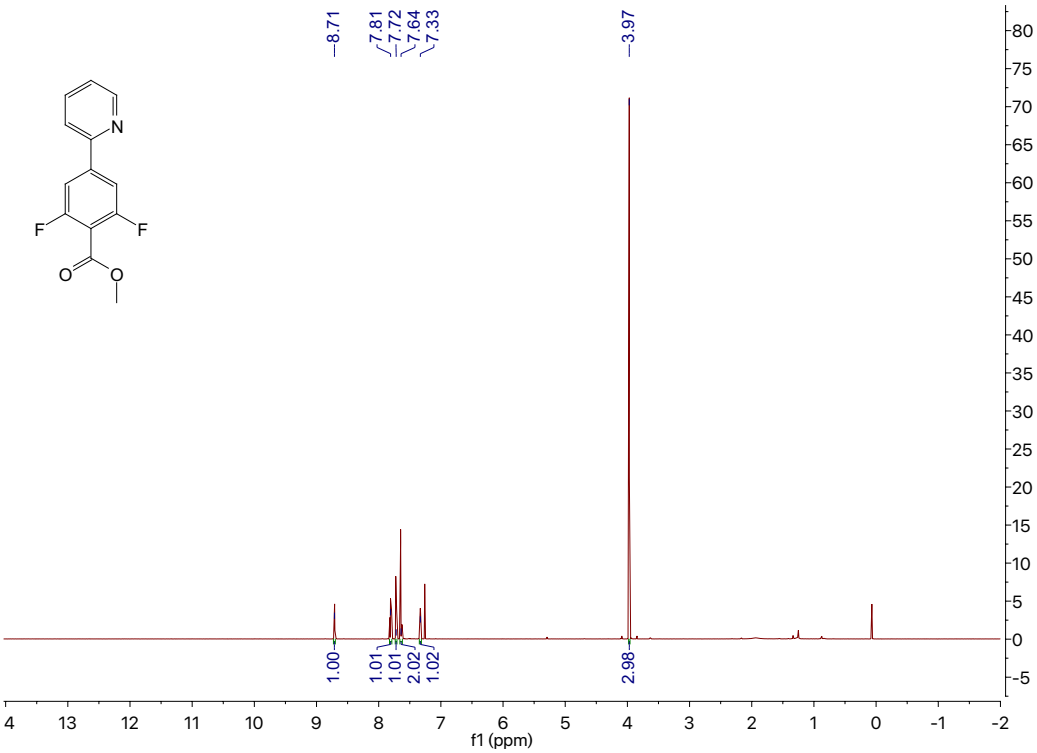
^{13}C (176 MHz, $CDCl_3$) — mixture of **75a** and **75b** (52 : 48)



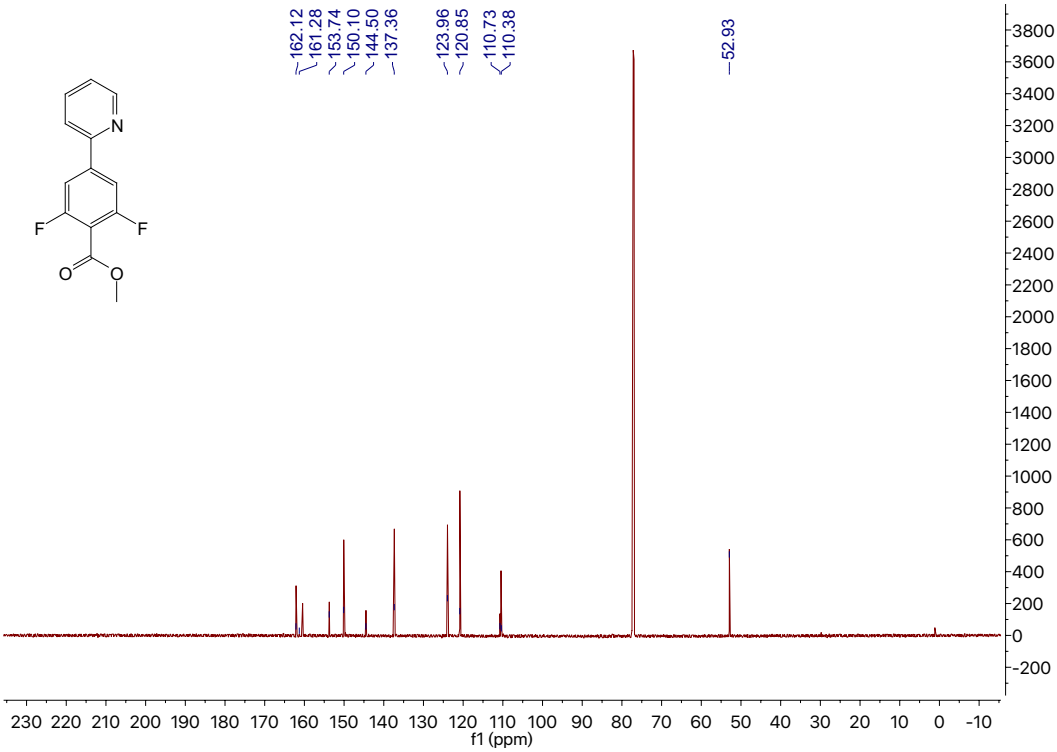
^{19}F (376 MHz, $CDCl_3$) — mixture of **75a** and **75b** (52 : 48)



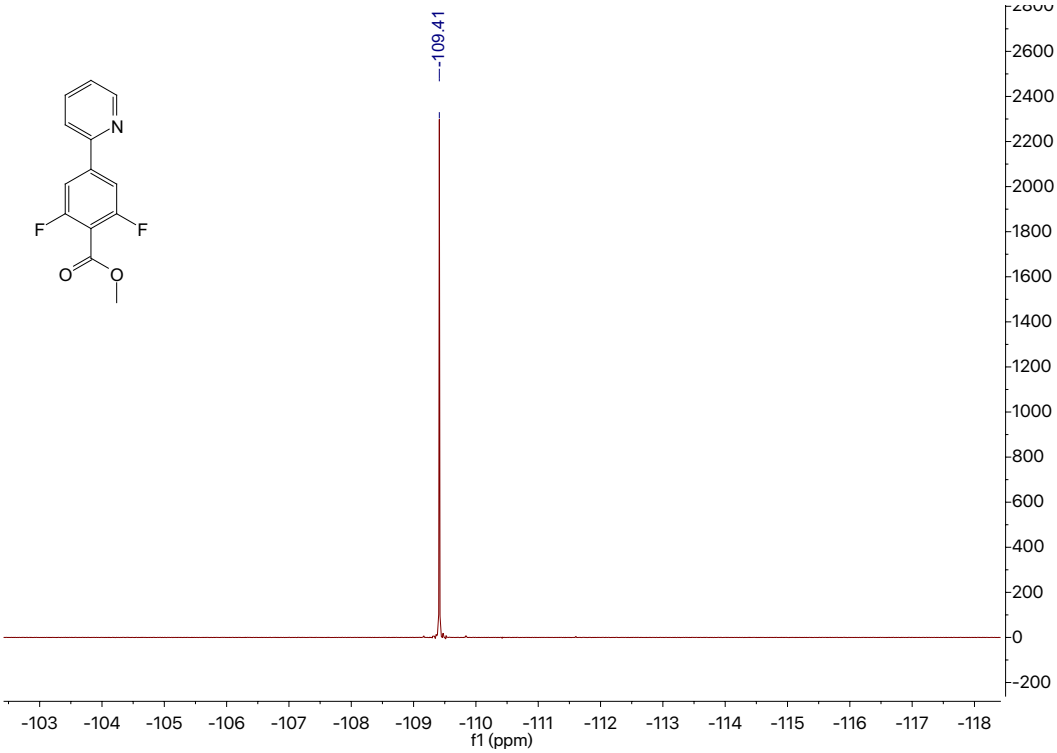
^{1}H (599 MHz, $CDCl_3$) — **75d**



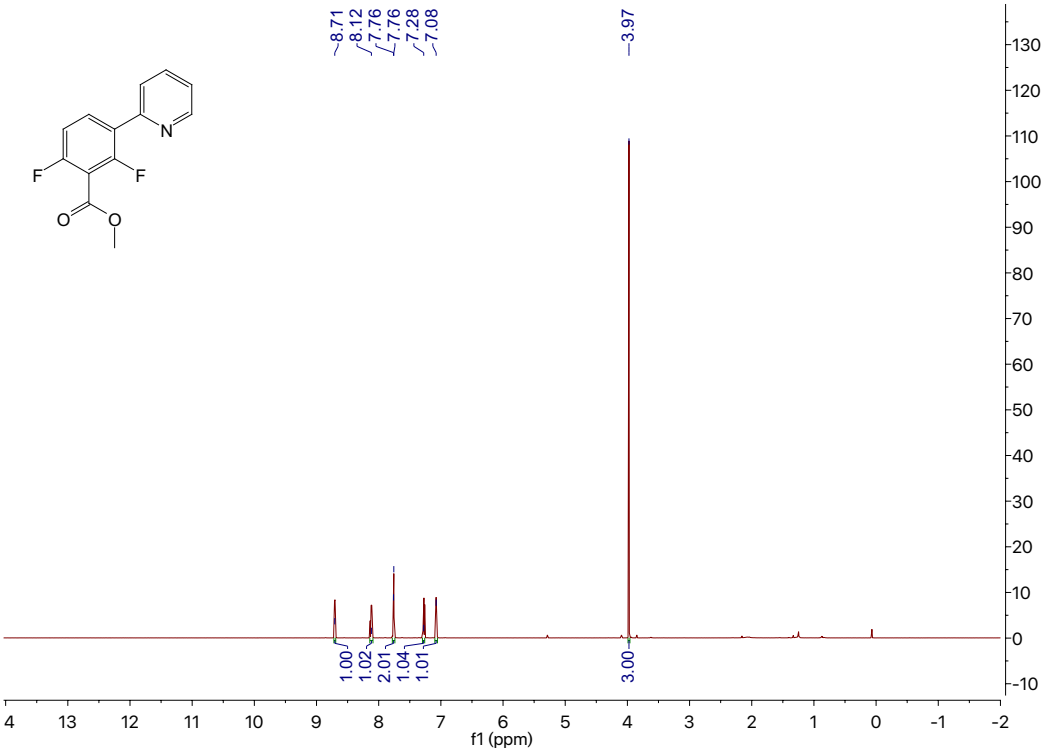
^{13}C (151 MHz, $CDCl_3$) — **75d**



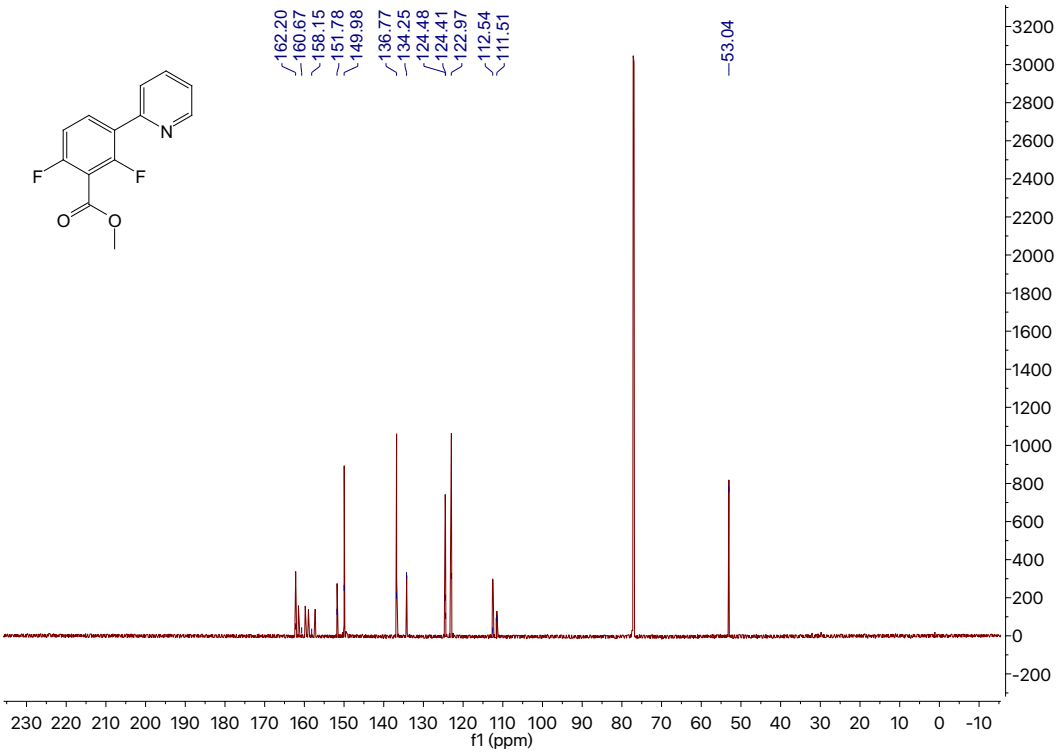
^{19}F (376 MHz, $CDCl_3$) — **75d**



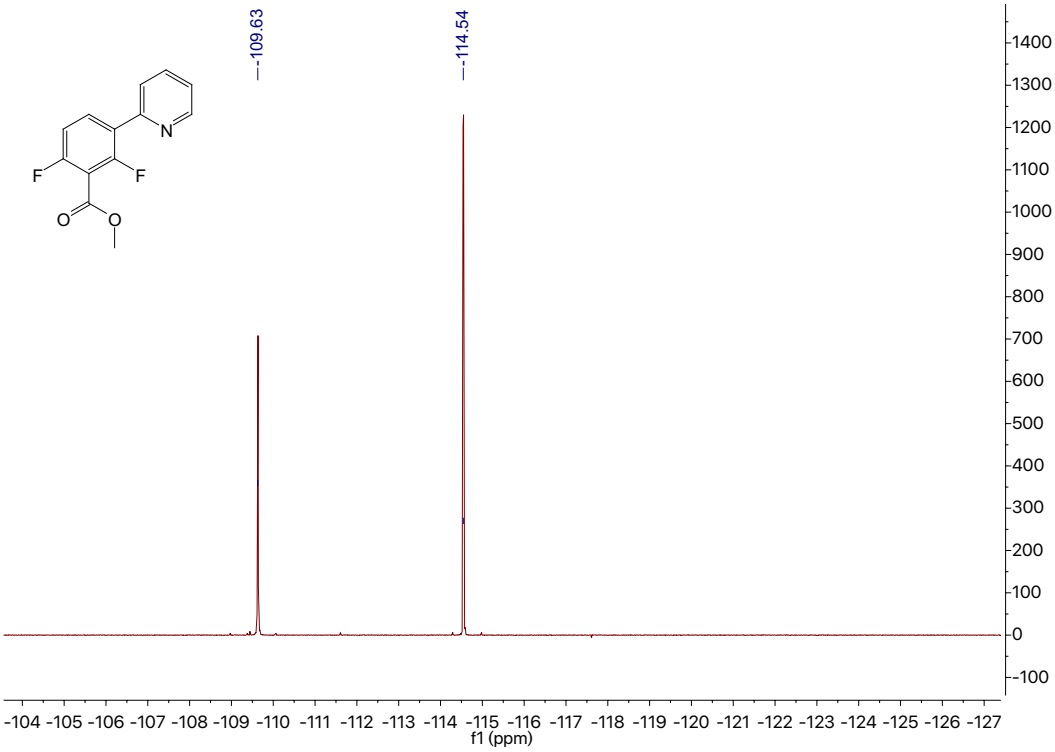
^{1}H (599 MHz, $CDCl_3$) — **75e**



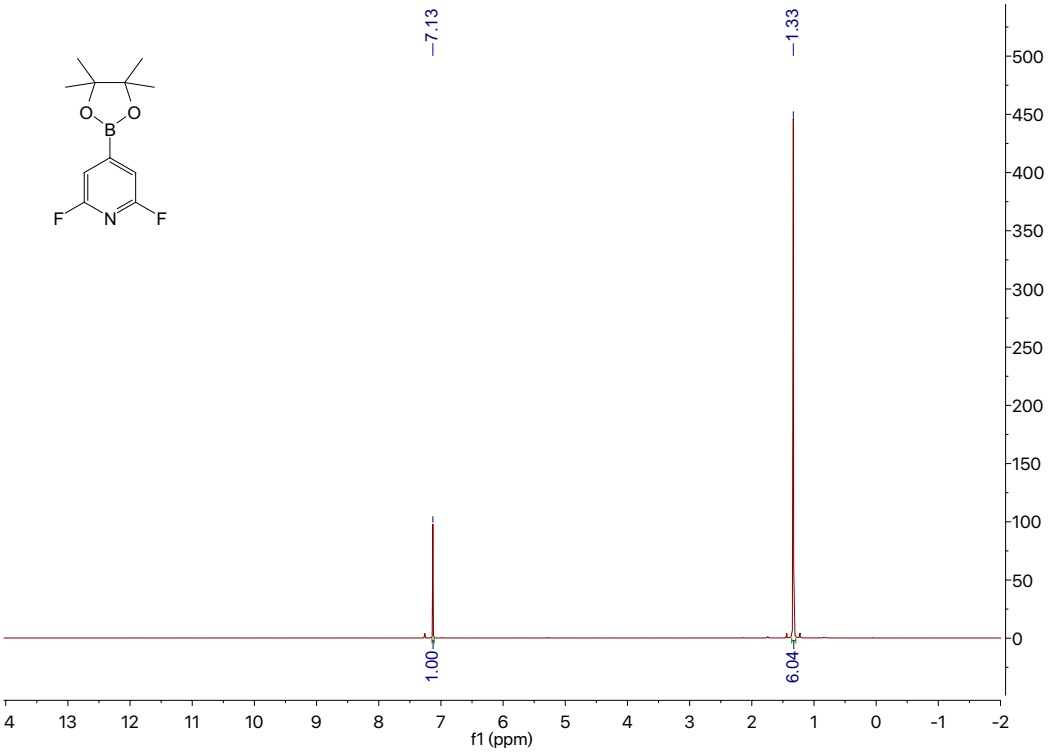
^{13}C (151 MHz, $CDCl_3$) — **75e**



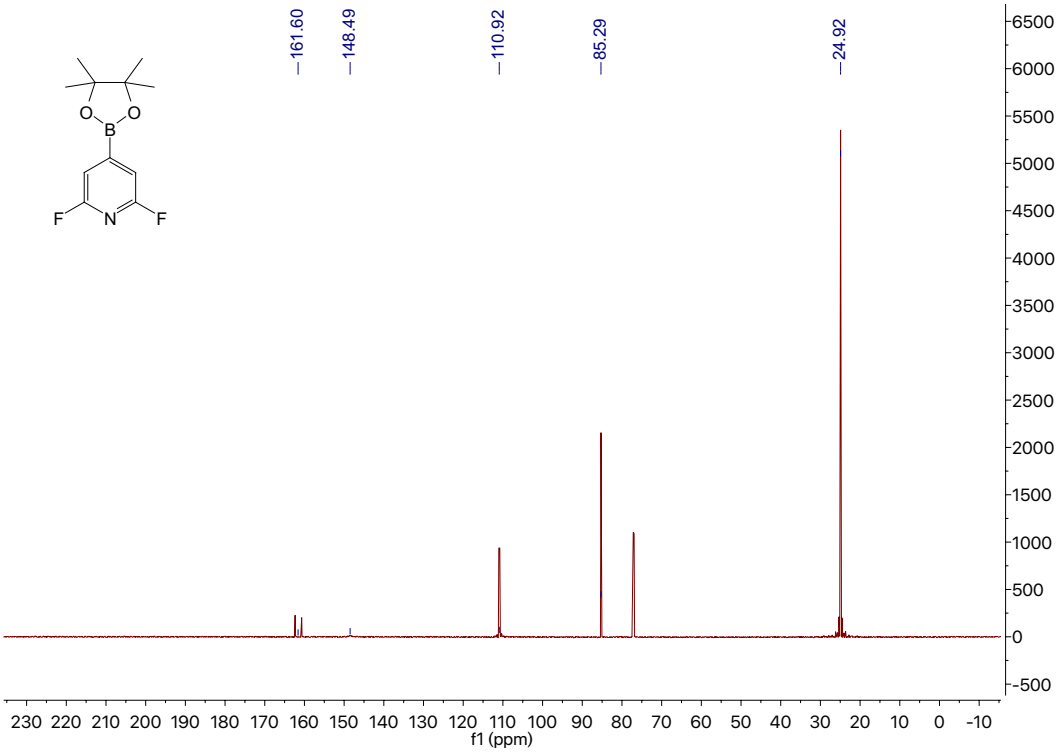
^{19}F (376 MHz, $CDCl_3$) — **75e**



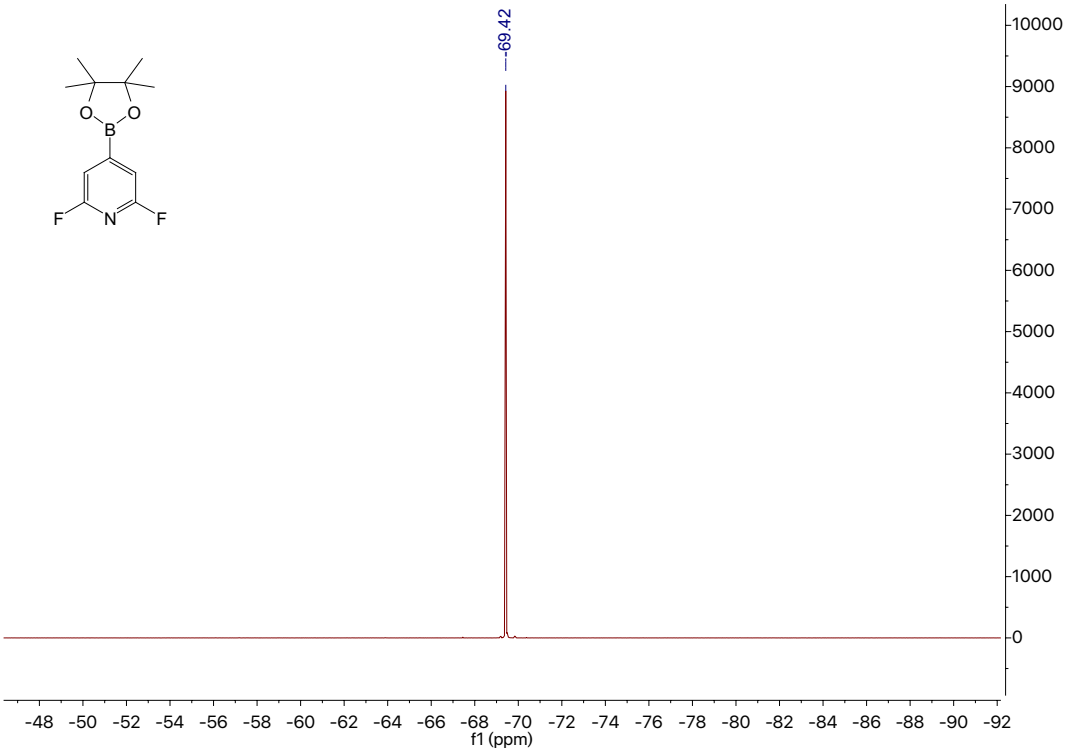
^{1}H (599 MHz, $CDCl_3$) — **76a**



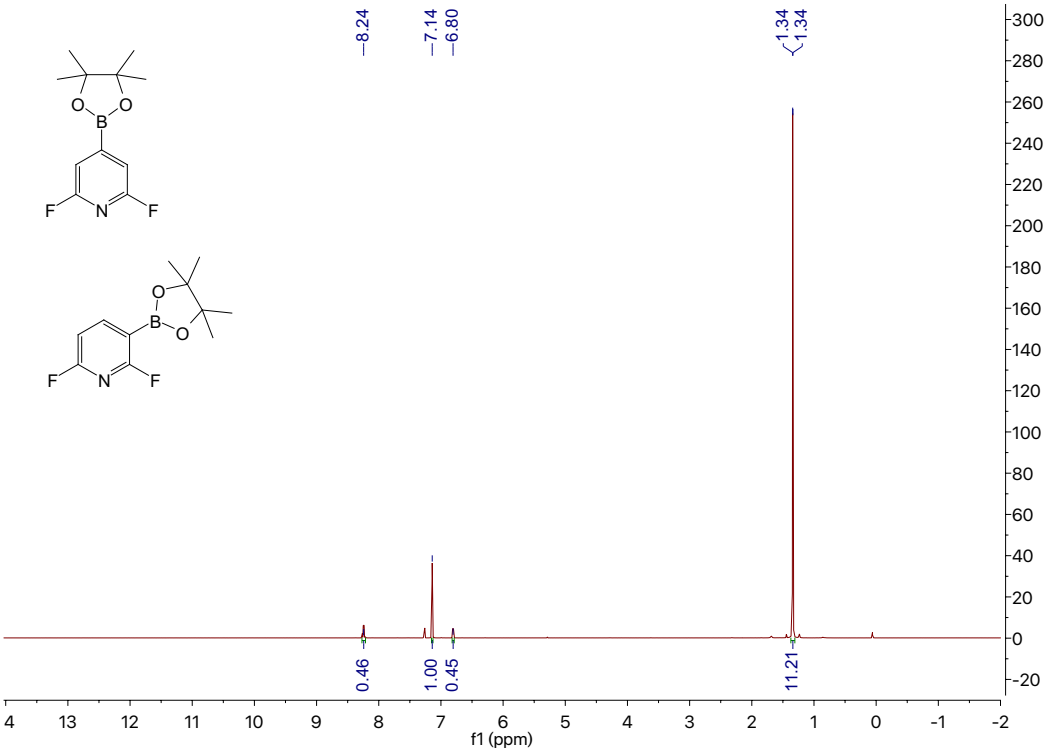
^{13}C (151 MHz, $CDCl_3$) — **76a**



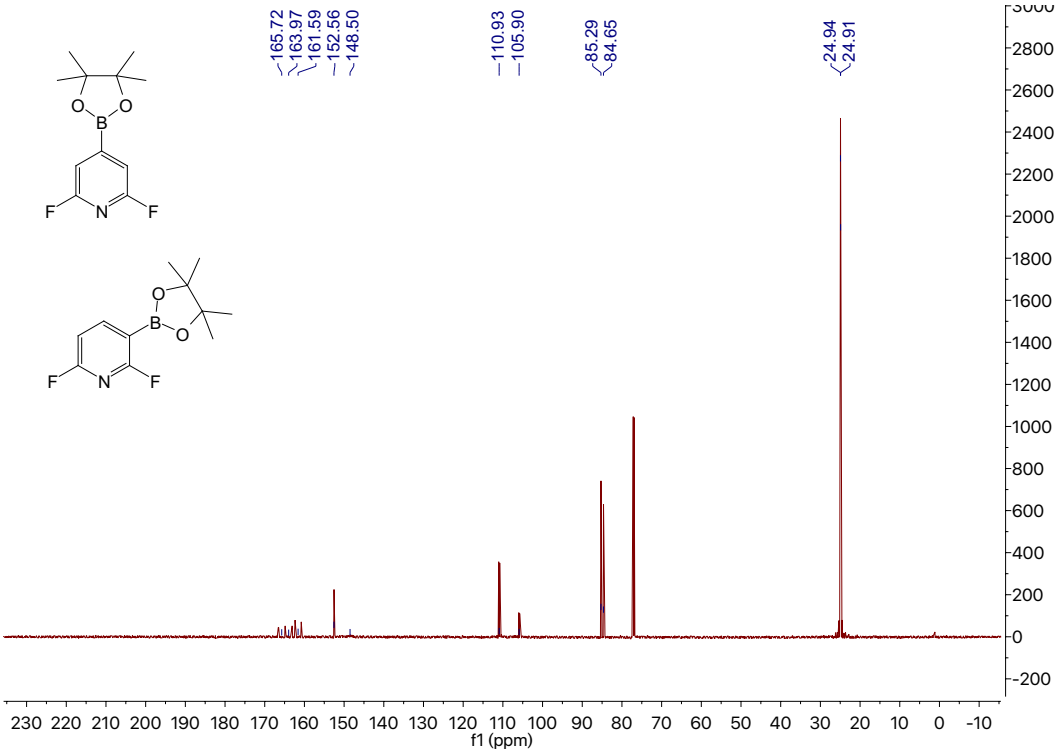
^{19}F (376 MHz, $CDCl_3$) — **76a**



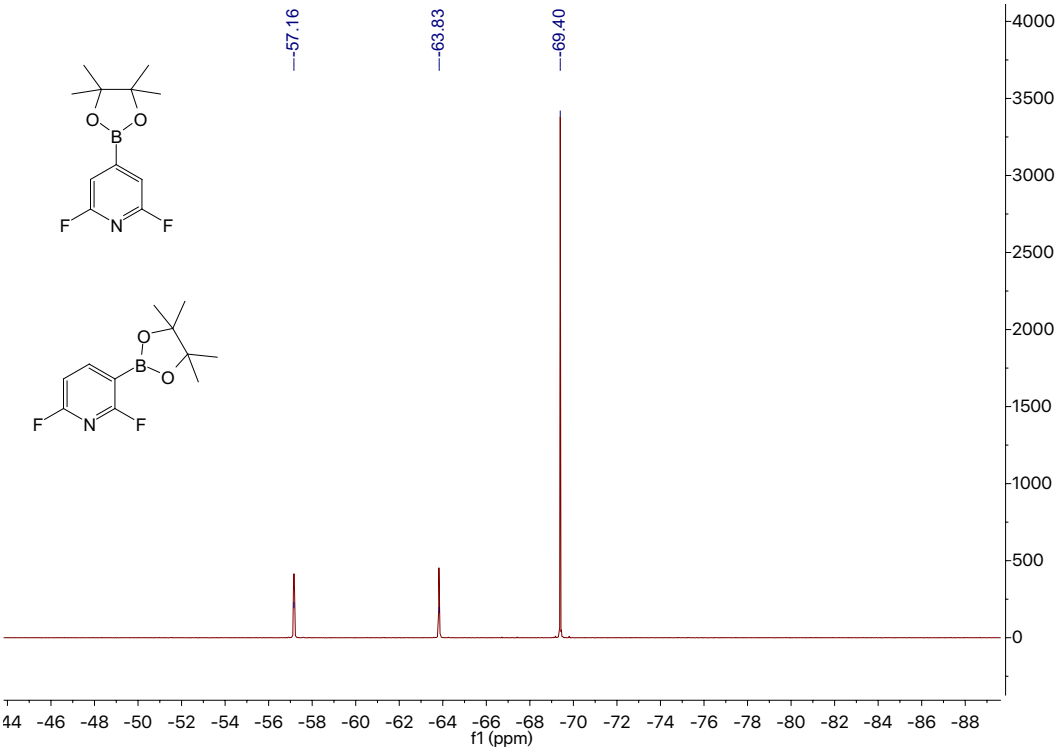
^{1}H (599 MHz, $CDCl_3$) — mixture of **76a** and **76b** (55 : 45)



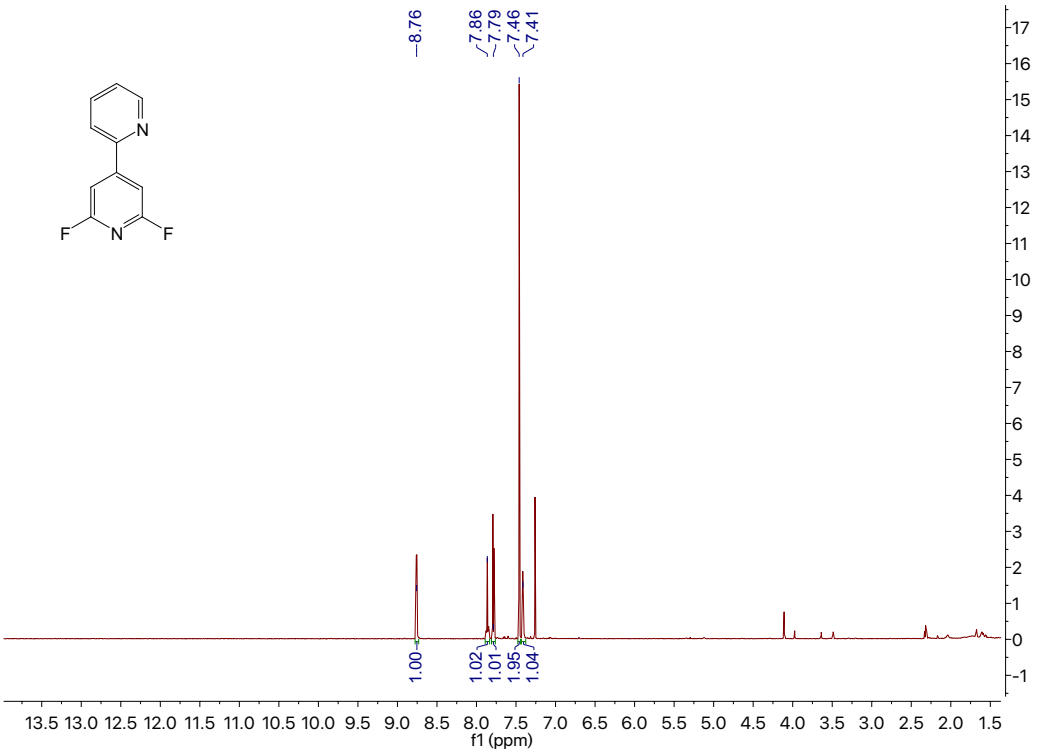
^{13}C (151 MHz, $CDCl_3$) — mixture of **76a** and **76b** (55 : 45)



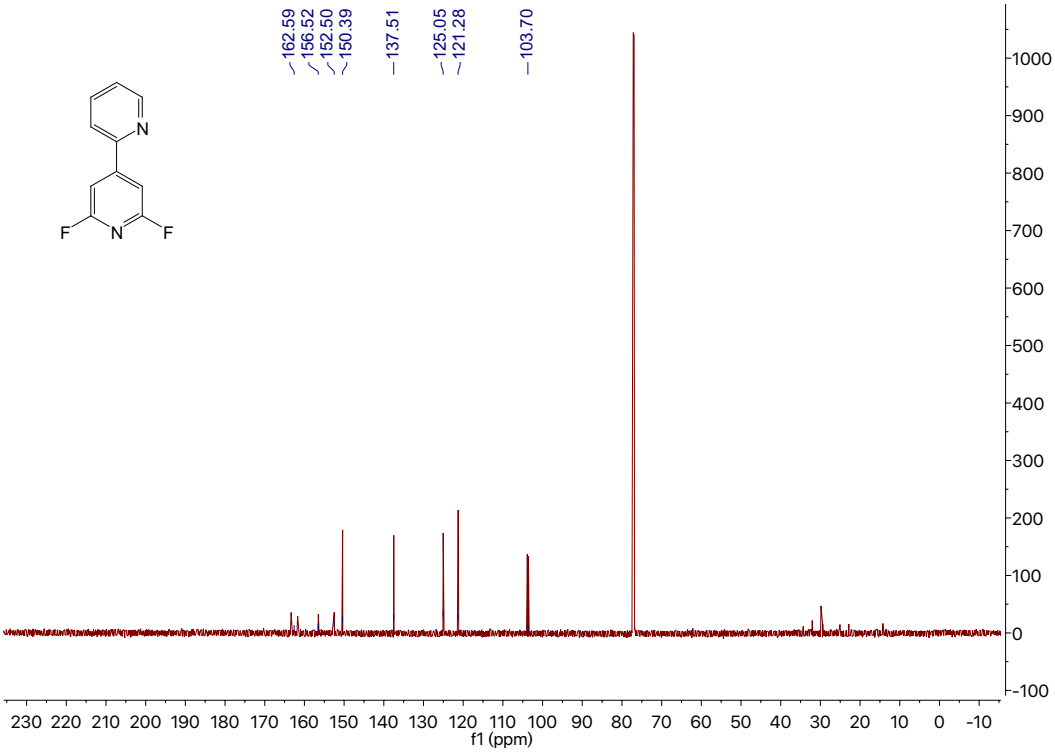
^{19}F (376 MHz, $CDCl_3$) — mixture of **76a** and **76b** (55 : 45)



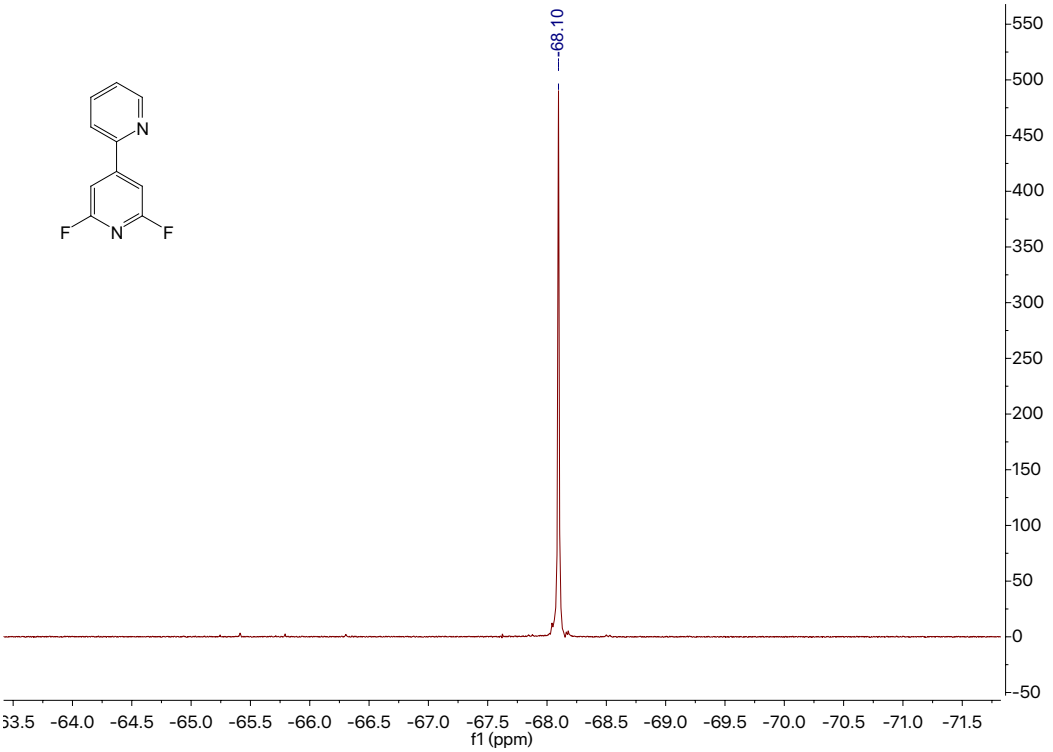
^{1}H (599 MHz, $CDCl_3$) — **76d**



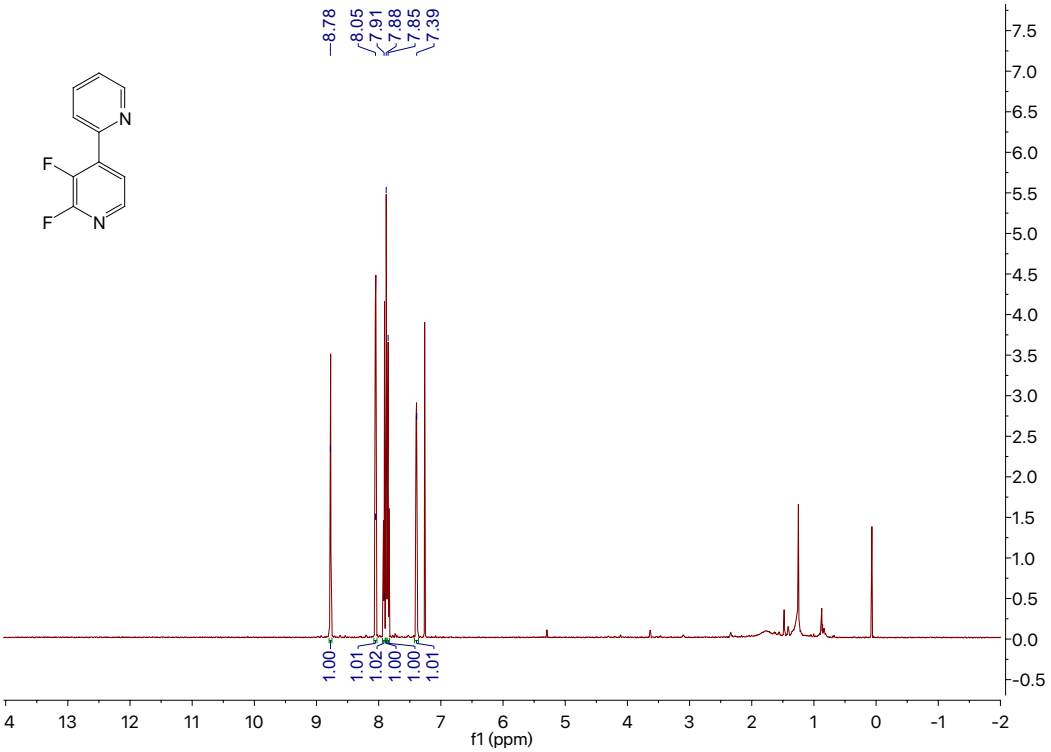
^{13}C (151 MHz, $CDCl_3$) — **76d**



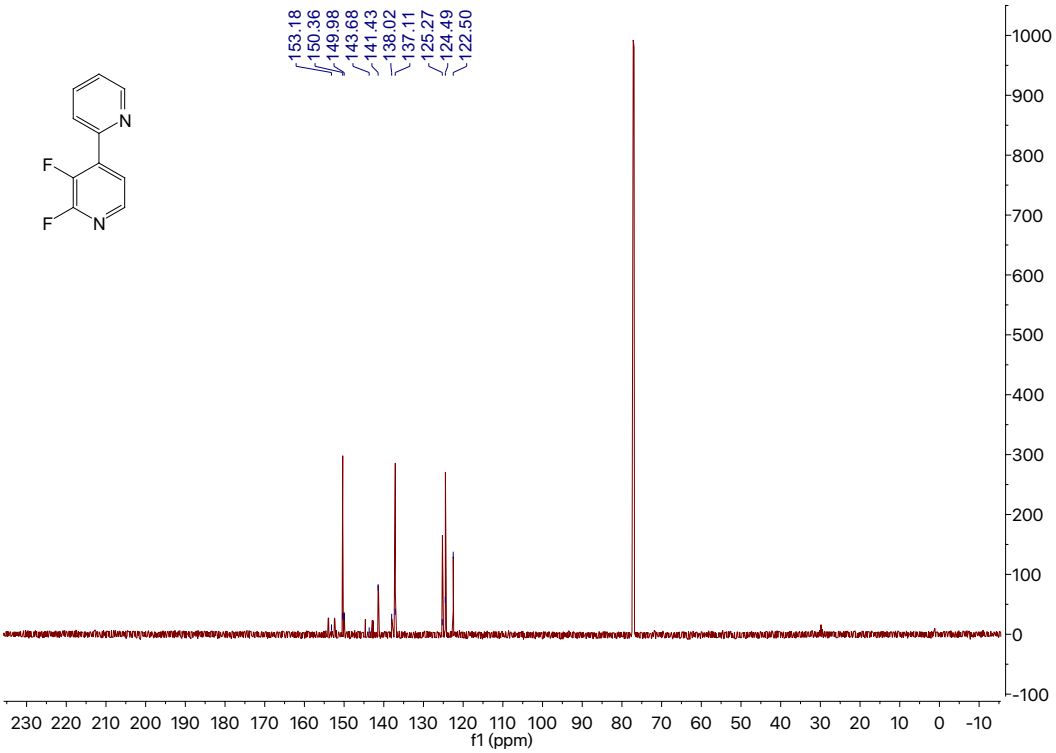
^{19}F (376 MHz, $CDCl_3$) — **76d**



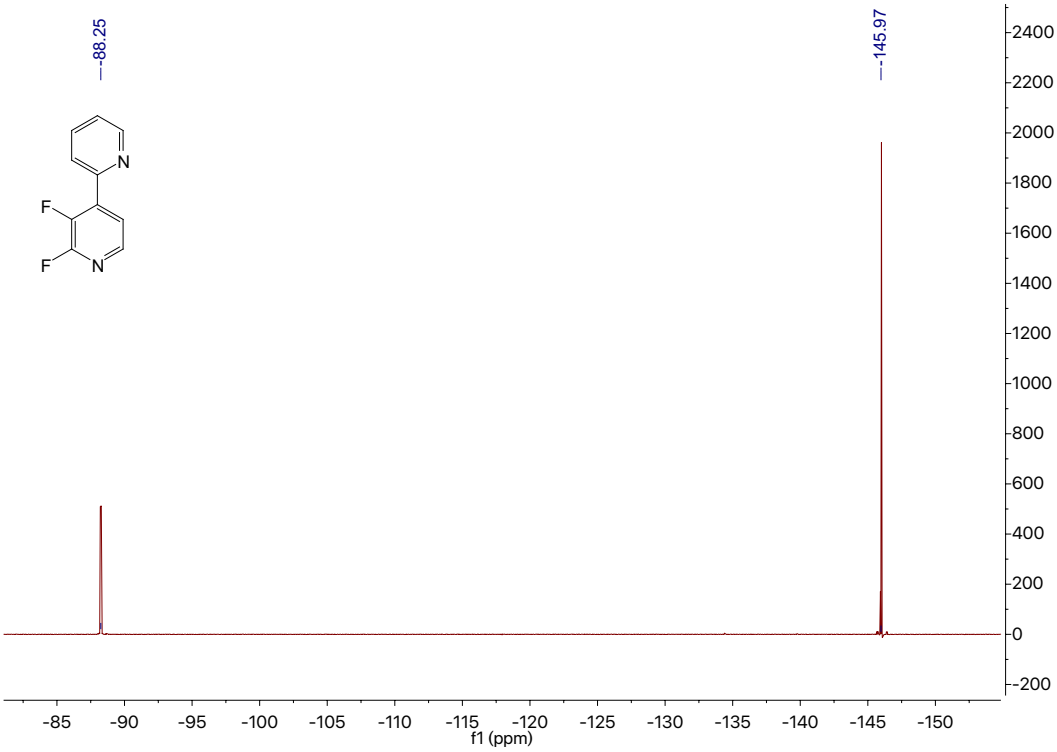
^{1}H (599 MHz, $CDCl_3$) — **80d**



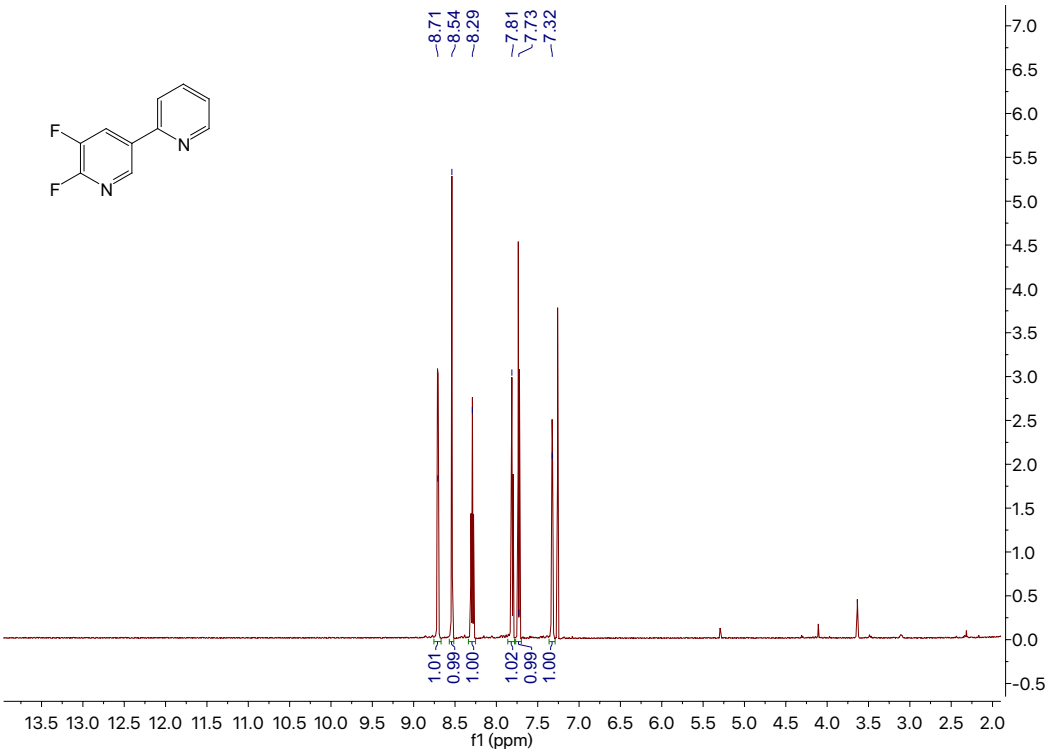
^{13}C (151 MHz, $CDCl_3$) — **80d**



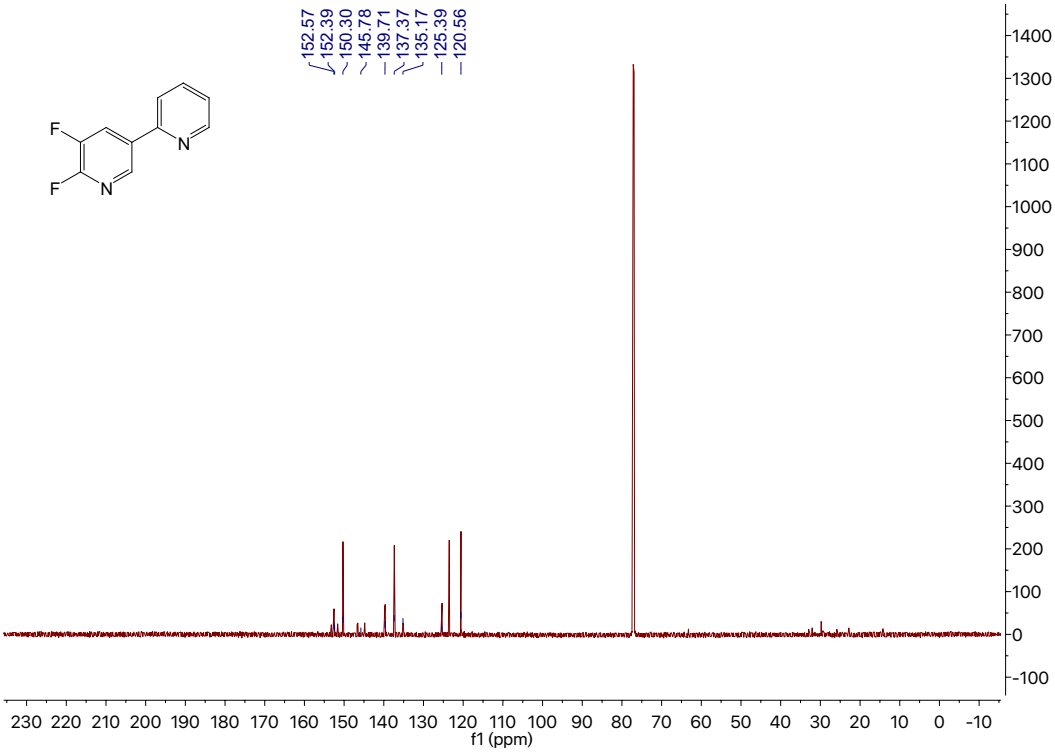
^{19}F (376 MHz, $CDCl_3$) — **80d**



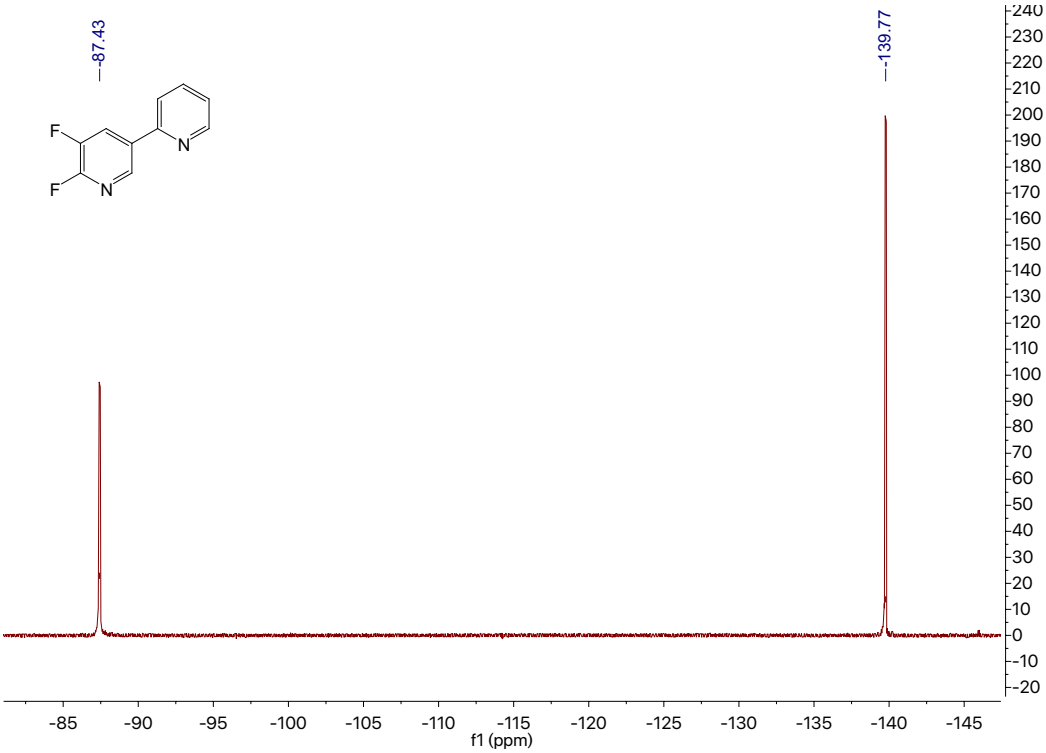
^{1}H (599 MHz, $CDCl_3$) — **80e**



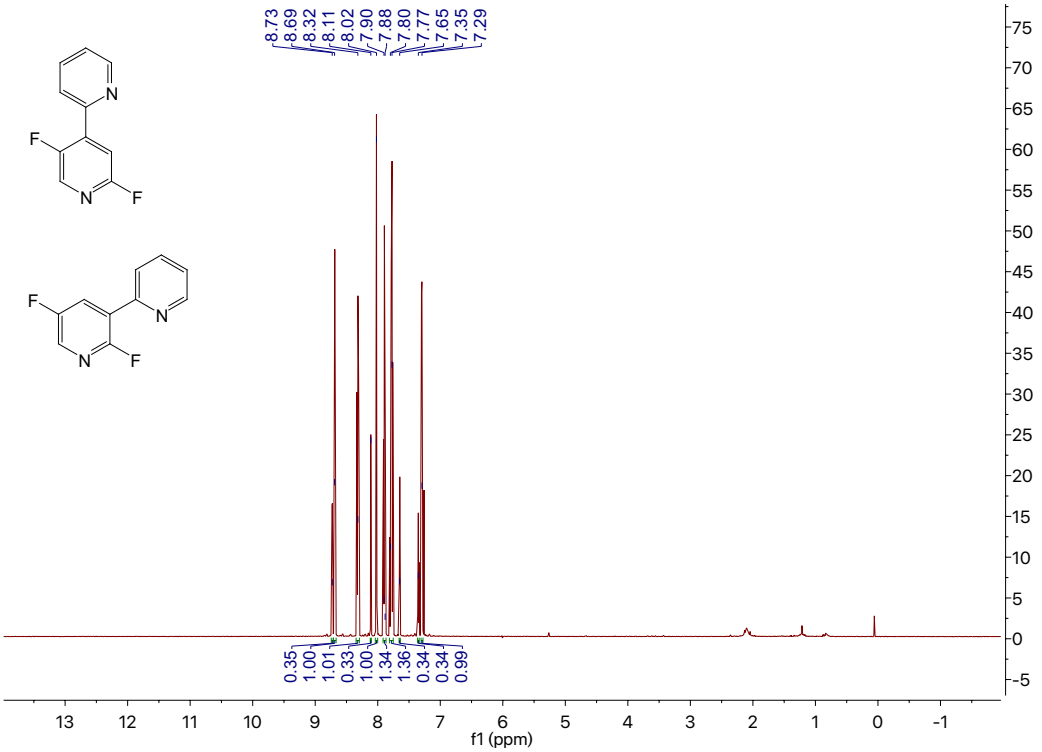
^{13}C (151 MHz, $CDCl_3$) — **80e**



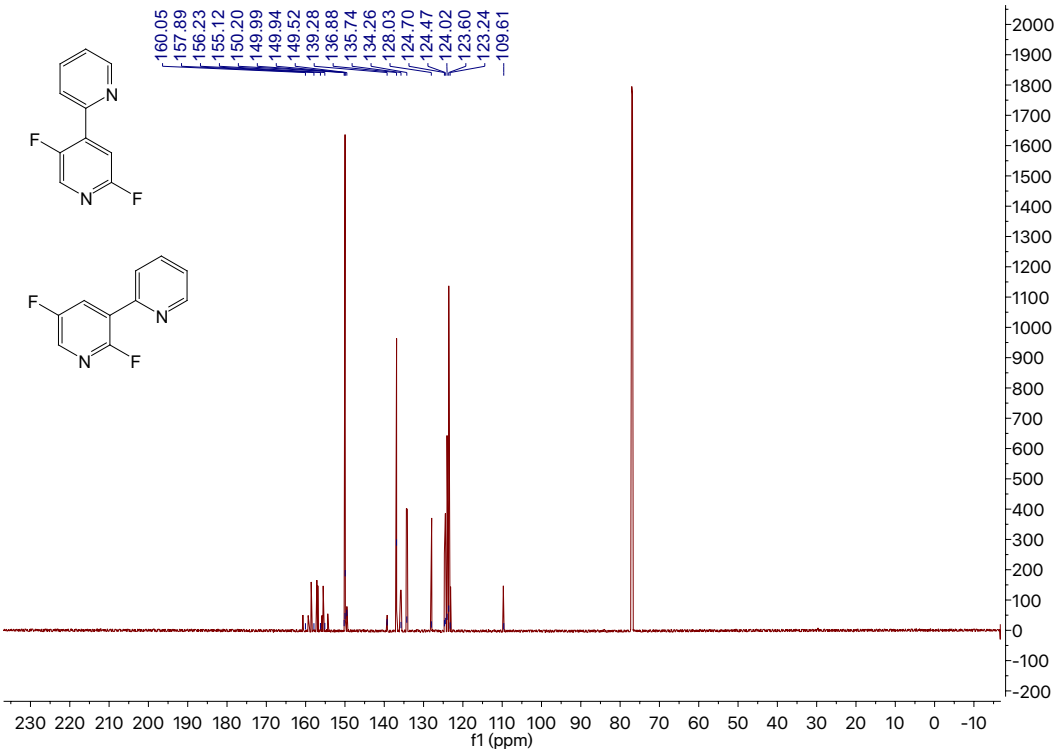
^{19}F (376 MHz, $CDCl_3$) — **80e**



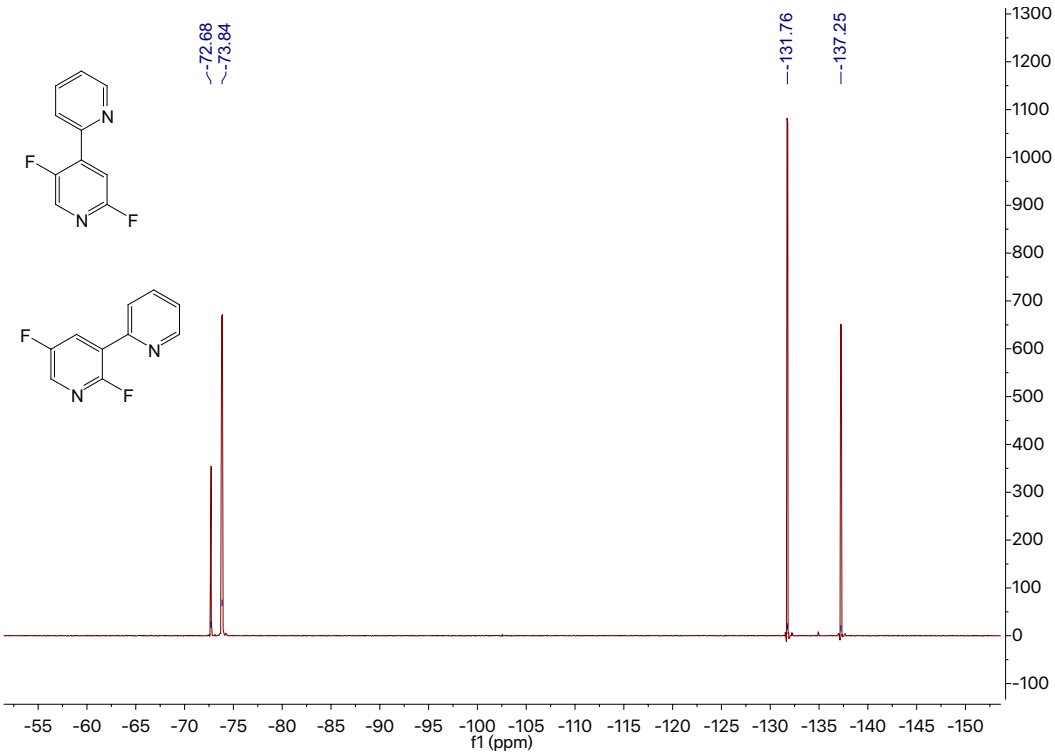
^{1}H (700 MHz, $CDCl_3$) — mixture of **81e** and **81f** (75 : 25)



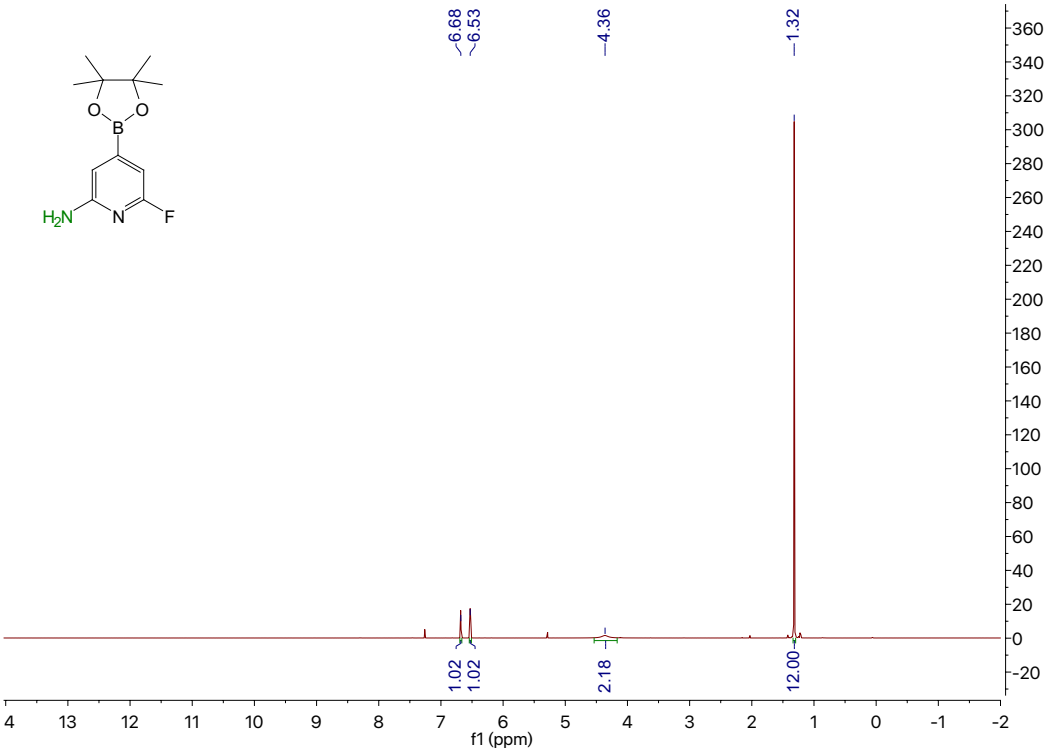
^{13}C (176 MHz, $CDCl_3$) — mixture of **81e** and **81f** (75 : 25)



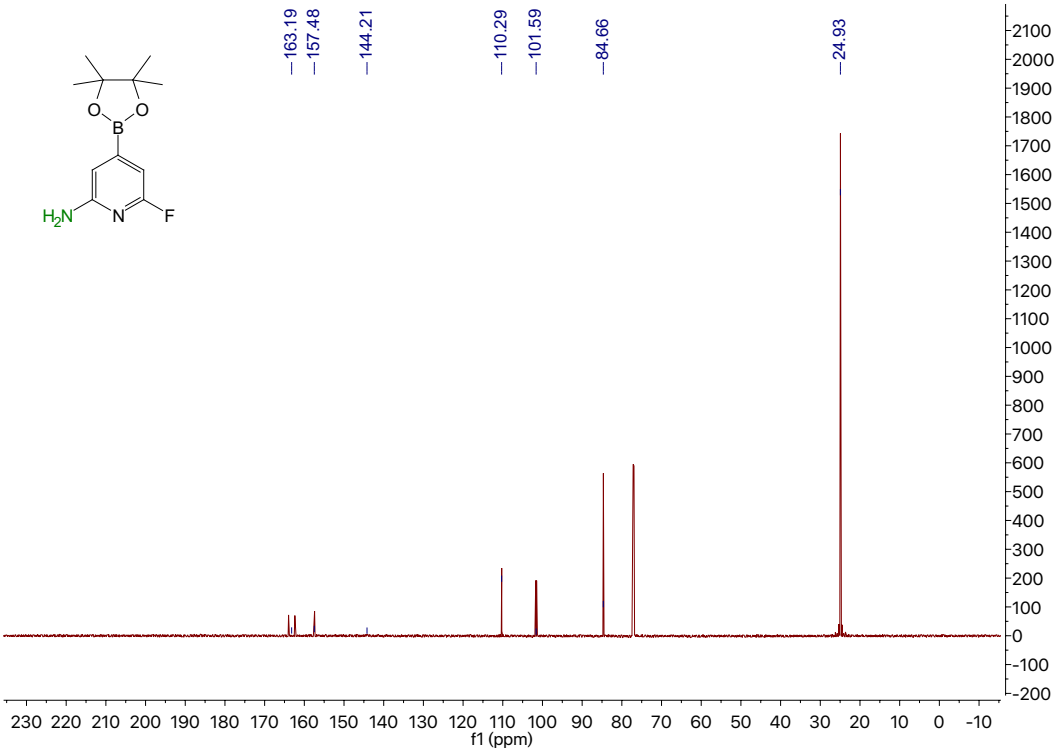
^{19}F (376 MHz, $CDCl_3$) — mixture of **81e** and **81f** (75 : 25)



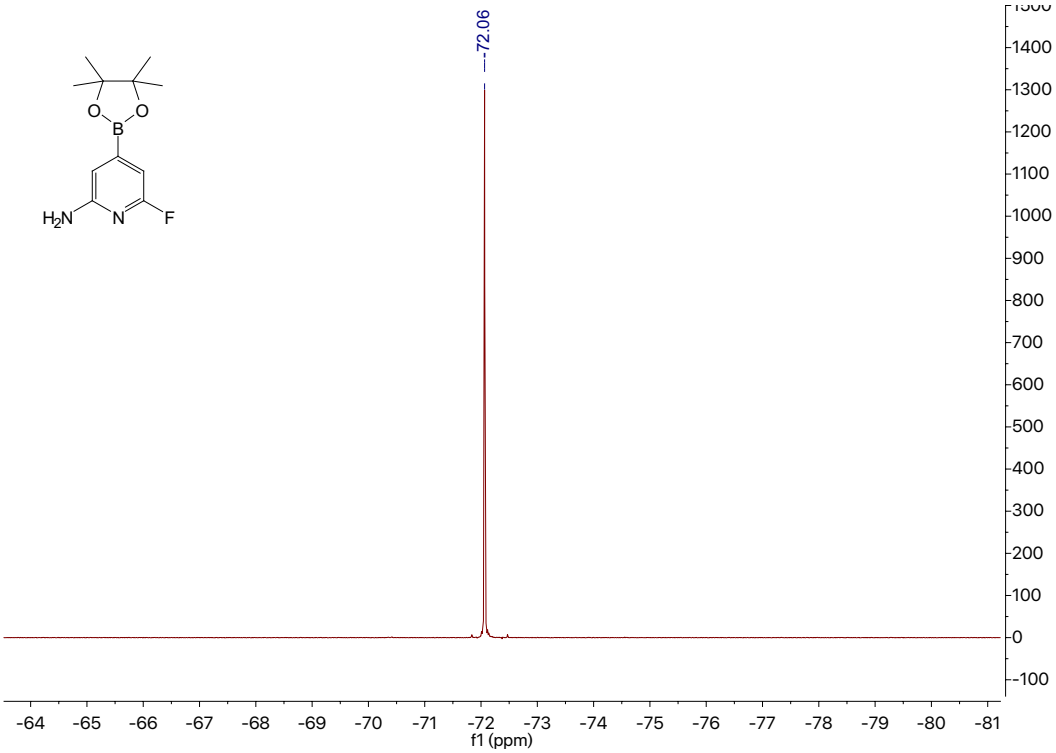
^{1}H (599 MHz, $CDCl_3$) — **82a**



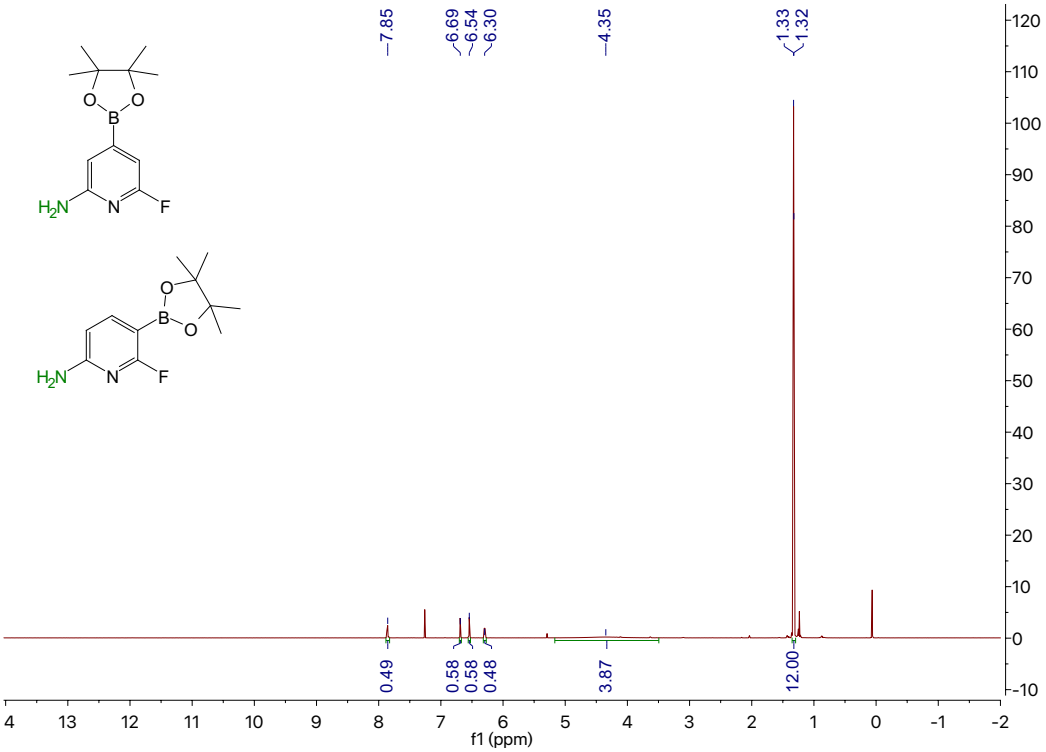
^{13}C (151 MHz, $CDCl_3$) — **82a**



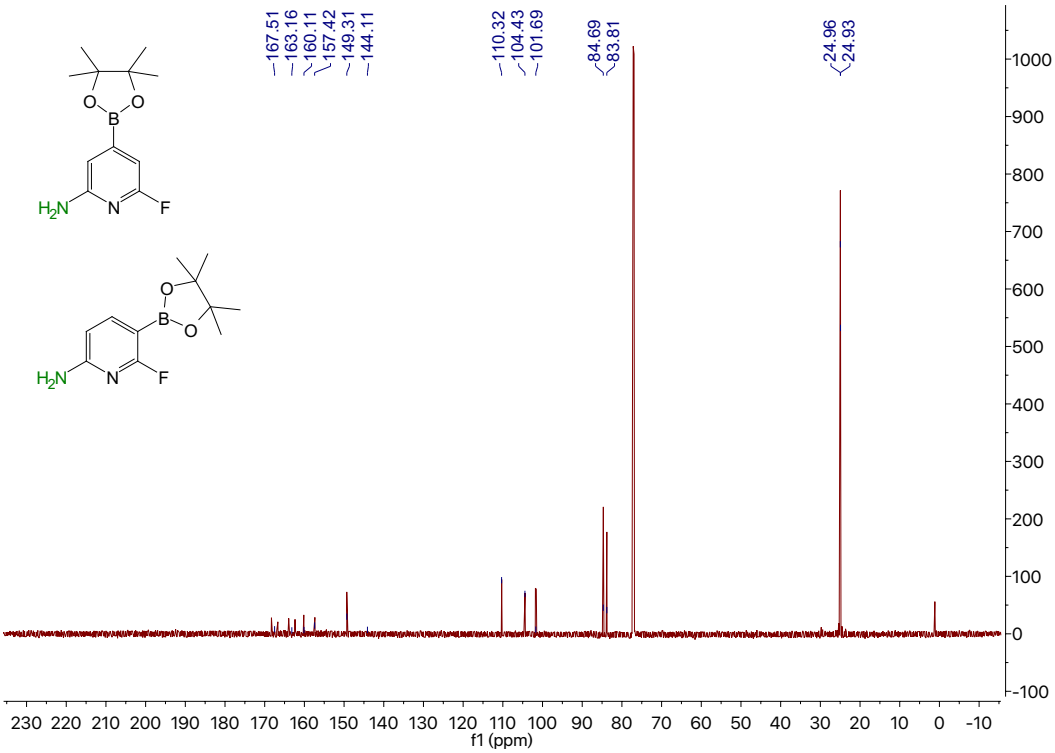
^{19}F (376 MHz, $CDCl_3$) — **82a**



^{1}H (599 MHz, $CDCl_3$) — mixture of **82a** and **82b** (54 : 46)



^{13}C (151 MHz, $CDCl_3$) — mixture of **82a** and **82b** (54 : 46)



^{19}F (376 MHz, $CDCl_3$) — mixture of **82a** and **82b** (54 : 46)